

**“The impact of Deep Brain Stimulation of the Subthalamic
nucleus on reward responsiveness in patients with Parkinson’s
disease”**

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Abbreviations

ACC – Anterior Cingulate Cortex

ADL – Activities of Daily Living

BDI – Beck Depression Inventory

CARROT – Card arranging reward responsivity objective test

DBS – Deep Brain Stimulation

DLPFC – Dorsolateral prefrontal cortex

GPe – Globus Pallidus externa

GPI - Globus Pallidus interna

HFS – High Frequency Stimulation

IT – Initiation Time

MT – Movement Time

PD – Parkinson's disease

SNpc – Substantia Nigra pars compacta

SNpr - Substantia Nigra pars reticulata

SRT – Simple Reaction Time

UPDRS – Unified Parkinson's Disease Rating Scale

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Overview

The main focus of this project is the impact of Deep Brain Stimulation (DBS) surgery on reward responsiveness in Parkinson's disease (PD). This project aims to investigate what the neuropsychological effects of this surgical treatment can teach us about the mechanism of stimulation and its effects on the underlying neural circuits that are damaged in this disease.

The first part of this project aims to review the evidence on apathy in Parkinson's disease. Studies published to date are discussed and critically reviewed, with reference to the occurrence of apathy in Parkinson's disease and the effects of neurosurgical intervention on the occurrence of apathy in Parkinson's disease.

The second part of this project aims to assess Parkinson's disease patients who have undergone Deep Brain Stimulation surgery for the treatment of the motor symptoms of the disease. Specifically, this study aims to assess the impact of Deep Brain Stimulation on reward responsiveness, as measured by patient's motor performances on a simple reaction time task and a card-sorting task.

The final part of this project is a critical appraisal of the research, reflecting on the research process; the strengths and weakness of the study, changes I would make to improve the study and how further research could build upon the results obtained here are discussed.

Part 1. Literature Review

“A Review of Apathy in Parkinson’s Disease”

Abstract

Apathy is defined as a primary loss of motivation in the absence of emotional distress, intellectual impairment or clouding of consciousness. High rates of apathy occur in Parkinson's disease (PD), with some authors suggesting that it is a core feature of the disease. The factors that influence the occurrence of apathy in PD are controversial, however some factors are consistently found to be associated with higher levels of apathy in this population, namely damage to the basal ganglia or frontal lobes; dopamine deficiency; dementia and hallucinations. The factors that do not influence the occurrence of apathy in PD are depression and severity of motor impairment caused by the disease. Deep brain stimulation (DBS) of the Subthalamic Nucleus (STN) is a surgical technique used to ameliorate the aberrant motor symptoms of PD. However, as well as influencing motor symptoms, STN DBS has been found to have effects on cognitive, affective and psychosocial functioning. The effects of STN DBS on apathy are unclear, with some studies finding evidence of worsening and others finding improvement of apathy. However the factors that have been suggested to influence the occurrence of apathy in these patients are increased age, longer pre-operative disease duration, and more severe motor symptoms. The frontal-subcortical circuits are a group of five parallel neural pathways, connecting the basal ganglia with the frontal lobes. Due to deterioration of the basal ganglia in PD, these circuits have been implicated in the motor and non-motor symptoms of the disease, including apathy. More research is required to develop our understanding of the effects of stimulation on apathy in PD and the neural circuits that underlie it.

Parkinson's disease (PD) is a progressive degenerative neurological disorder resulting from the degeneration of the dopamine producing cells in the substantia nigra pars compacta, which forms part of the basal ganglia (Crossman & Neary, 2000). Apathy is common in PD and is one of the non-motor symptoms of the disease. In this review the pathophysiological model of PD, treatment approaches used and the motor and non-motor treatment outcomes will be discussed by way of introduction to PD. The main focus of this paper is apathy in PD and the influence of DBS on the occurrence and course of apathy in PD patients. This is an area of some debate within both academic and clinical arenas, as there is much conflicting evidence as to the nature of apathy in these populations. However, there is consistent evidence regarding the negative impact of apathy in PD, both for patients who have undergone surgical treatment and those who have not, and for their families. This highlights the need for further study and reflection upon the impact of treatments, including deep brain stimulation surgery, on apathy, as this the potential impact of surgical intervention may constitute an ethical consideration on the part of clinicians and an additional factor in the decision to undergo surgery for patients and families. The current literature on apathy in PD will be discussed in relation to its prevalence and presentation, the relationship of apathy to other PD symptoms, and the neural pathways common to both apathy and the motor symptoms of PD. This leads to the main focus and research questions of this review; "What factors influence the development of apathy in PD?" and "Does deep brain stimulation of the subthalamic nucleus influence apathy in PD?".

Research method

For the purposes of this review, a structured Pubmed search was performed on articles up to May 2008. The following key words were used; apathy; Parkinson's disease; subthalamic nucleus; deep brain stimulation; treatment; function. These studies were reviewed by one investigator (AH).

1.0 Parkinson's disease

The basal ganglia are a group of subcortical nuclei; the striatum is the anatomical term for the caudate nucleus and putamen, which are the input areas of the basal ganglia, while the internal segment of the globus pallidus and the substantia nigra pars reticulata (SNr) are the output areas of the basal ganglia (Crossman & Neary, 2000). Figure 1(a) illustrates the location of the striatum and related structures. When these areas are damaged they give rise to a group of disorders, termed basal ganglia disorders (Crossman & Neary, 2000). Parkinson's disease (PD) is a degenerative neurological disorder resulting from the degeneration of dopamine producing cells in the Substantia Nigra pars compacta (SNc) (Brown & Jahanshahi, 1991). The major symptoms of PD include tremor, rigidity, bradykinesia (slowness of movement) and postural abnormality. Other common symptoms include balance and walking problems, akinesia (poverty of movement) micrographia (reduced size of hand-writing), dysphonia (reduced vocal volume), masked faces and fatigue (Gibb & Lees, 1989). Prevalence rates of PD can vary widely according to diagnostic criteria and other inclusion factors, ranging from approximately 10 in 100,000 to 405 in 100,000 (Korell & Tanner, 2005). Risk factors for PD have been identified, including increasing age and male gender; while protective

factors include smoking and the use of non-steroidal anti-inflammatory drugs (ibid).

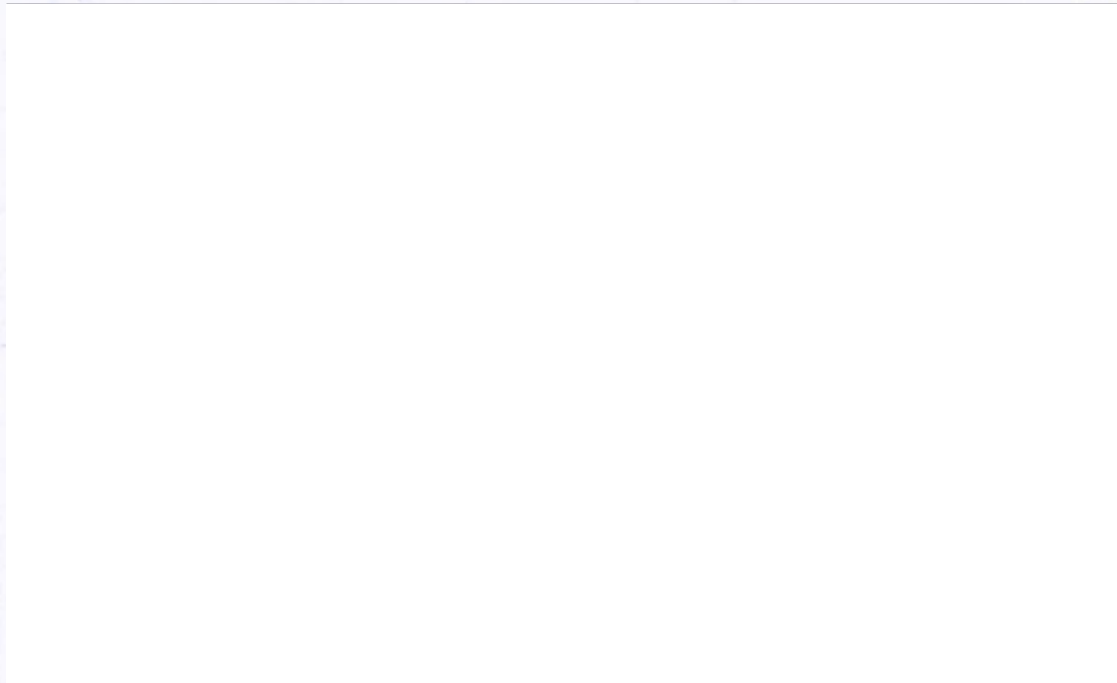


Figure 1(a). The Striatum and related structures (Bear, Connors & Paradiso, 2001)

1.1 The Pathophysiological Model of PD

1.1.1 The Frontal-subcortical circuits

The symptoms of PD result from the depletion of the dopamine pathways of the pars compacta subdivision of the substantia nigra (Crossman & Neary, 2000). As a result, the balance of activity in the direct and indirect pathways of the frontal cortex are altered leading to the inhibition of cortical motor areas resulting in the manifestation of bradykinesia and akinesia in PD (Alexander, De Long & Strick, 1986). The motor circuit involved in PD is one of the five, comprising the frontal-subcortical circuits between discrete areas of the striatum and the distinct parts of the frontal cortices. The motor circuit mediates motor control, while the remaining four circuits mediate oculomotor control (oculomotor circuit), executive function (dorsolateral prefrontal

circuit), emotion and social behaviour (lateral orbitofrontal) and motivation (anterior cingulate circuit) (Alexander et al, 1986). Figure 1(b) illustrates these circuits.

Figure 1(b). The “Motor”, “Executive”, “Emotional and “Motivational” circuits respectively, from Alexander, De Long & Strick’s (1986) Model of the frontal-subcortical circuits
DL: Dorsolateral; DM: Dorsomedial; VL: ventrolateral; VA: ventroanterior; VM: ventromedial

1.1.2 The Subthalamic Nucleus

The Subthalamic Nucleus (STN) is a group of cells that, along with the Globus Pallidus externa (GPe), forms the indirect pathway between the basal ganglia and frontal cortex, and alters the output of the basal ganglia to the cortex (Alexander et al, 1986). In the healthy basal ganglia projections from the striatum inhibit the lateral pallidum, which in turn disinhibit the STN, resulting in the discharge of subthalamic neurons and the activation of medial pallidal and nigral neurons and the inhibition of thalamic and cortical neurons (Crossman & Neary, 2000). This activity, therefore, leads to the inhibition of unwanted movements in the healthy basal ganglia. Figure 1(c) illustrates

the pathophysiological model of Parkinson's disease in comparison with healthy function.

In PD there is excessive excitatory drive from the Subthalamic nucleus (STN) to the Globus Pallidus interna (GPi), coupled with reduced inhibitory input from the Globus Pallidus externa (GPe) to the GPi, the result of which is excessive inhibitory outflow from the GPi to the ventral thalamus, leading to the under-activation of the frontal cortical areas (Cummings, 1993). Evidence for this frontal underactivation is provided by imaging studies in PD (Jahanshahi et al, 1995; Playford et al, 1991). The overactive STN and GPi and the alteration of balance of activity in the direct and indirect pathways are associated with bradykinesia and akinesia as well as dyskinesias (involuntary movements) in PD (Crossman & Neary, 2000).



Figure 1(c). The pathophysiological model of Parkinson's disease compared with healthy function (Cenci, 2007). The basal-ganglia-thalamocortical circuits in a normal state (a) and in the untreated parkinsonian state (b). Red, green and yellow lines indicate glutamatergic, GABAergic and dopaminergic pathways, respectively. Increased activity in the average activity rate of specific projection pathways are shown as thickening and decreased activity is shown as thinning of the corresponding lines compared with the normal state.

Key: GPe, external segment of the globus pallidus; GPi, internalsegment of the globus pallidus
SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata;
STN, subthalamic nucleus.

Therefore, patients with PD experience a disruption of the frontal-subcortical circuits due to a reduction of dopamine in the substantia nigra pars compacta (SNpc) resulting in alteration of the functioning of both the direct and indirect striatal pathways.

1.3 Treatment of PD

1.3.1 Drug Treatment

Levodopa is the most favoured drug for the treatment of PD symptoms. It acts to relieve the motor symptoms of PD as it is a metabolic precursor of dopamine and is therefore converted to dopamine, resulting in the normal functioning of the striatum and the reduction of symptoms (Crossman & Neary, 2000). However, there are disadvantages to treatment, as responsiveness to Levodopa lasts approximately five years, after which the effectiveness of the drug is significantly reduced (Limousin, 1998). Other disadvantages include side-effects of Levodopa treatment, including drug-induced dyskinesias (involuntary movements) and related motor fluctuations (Almedia & Hyson, 2008).

1.3.2 Surgical Treatment

Surgical treatments for PD include stereotaxic neurosurgical procedures involving Deep Brain Stimulation (DBS) of specific striatal areas, including the Subthalamic Nucleus (STN) and the Globus Pallidus interna (GPi), and the lesioning of specific areas, such as the GPi in Pallidotomy, or the STN in subthalamotomy or the Thalamus in Thalamotomy (Speelman, 1991). The surgical treatment focused upon in this review is DBS of the STN, which aims to alter the pathological basal ganglia outflow with high frequency stimulation of the STN leading to an improvement of PD motor symptoms,

namely bradykinesia, tremor, rigidity and also improvement of dyskinesias (Limousin et al, 1995). Improvement in PD symptoms with STN DBS treatment have been reported at twelve months post-surgery, however benefits can also be sustained for several years (Rodriguez-Oroz et al, 2005). Liang et al (2006) in their long term follow-up study of patient's with advanced PD who underwent bilateral STN DBS found that this surgery was an effective long term therapy.

DBS is an invasive surgical procedure involving the insertion of electrodes into the basal ganglia through the cranium. These electrodes are attached, via electrical leads which are placed beneath the skin of the scalp and neck, to a pace-maker like device called a neurostimulator, which is inserted beneath the skin of the chest of the patient. The neurostimulator may be activated and deactivated through the use of the separate control device, which when placed on the chest above the neurostimulator alters the electrical activity in the electrodes in the basal ganglia.

DBS is, therefore, a highly invasive surgical procedure. Patients are selected for surgery according to clinical criteria, namely diagnosis of PD, stage and severity of PD, as determined by Hoen and Yahr criteria and Unified Parkinson's Disease Rating Scale. However, general health and ability to undergo a prolonged surgical procedure in a conscious state are also necessary to be eligible for DBS.

Although the procedure of STN DBS surgery is becoming increasingly refined and our understanding of the mechanism of how STN stimulation functions to ameliorate the motor symptoms of PD is still unclear. It has been hypothesised that stimulation acts as a

functional lesion, causing disruption of the pathological basal ganglia output to the cortex.

STN DBS can improve all PD motor signs including to a lesser extent posture and balance problems (Pollack et al, 1998). PD motor symptoms are more improved by STN DBS than other surgical procedures, such as pallidotomy (Adam & Blanchette, 2004). However, although significant motor benefits of STN DBS have been reported, potential adverse effects of the surgery can be problematic. Adverse effects, namely non-motor outcomes including cognitive deterioration and behavioural disturbances can occur post-operatively in the short term, up to five years after surgery.

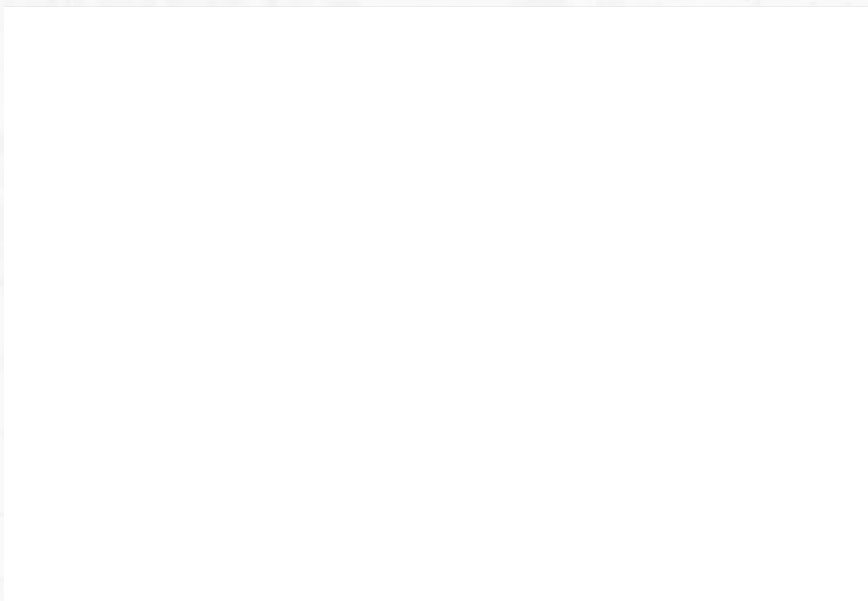


Figure 1(d). The location of electrodes and stimulator in deep brain stimulation of the subthalamic nucleus (Medtronic, 2006).

1.4 Non-motor outcomes of Subthalamic nucleus stimulation

Although STN DBS results in improvement of motor symptoms and quality of life of the patients, chronic stimulation has been found to have adverse effects on several areas of

functioning, leading to cognitive deficits (Funkiewiez et al, 2004) and behavioural and psychiatric complications (Rodriguez-Oroz, et al 2005).

1.4.1 Cognition and executive function

Studies of the cognitive outcomes of STN DBS are mixed, however a number of deficits in cognitive functions are consistently apparent, namely verbal memory (Alegret et al, 2001; Morrison et al, 2000; York et al, 2007), and visual memory (Saint-Cyr et al, 2000). Consistent deficits have also been found in phonemic verbal fluency (Alegret et al, 2001; Saint-Cyr et al, 2000), semantic verbal fluency (Alegret et al, 2001; Morrison et al, 2000; Saint-Cyr et al, 2000) and in visuospatial functioning (Alegret et al, 2001). Deficits have been found in executive functioning after STN DBS surgery, specifically in set-shifting, (Alegret et al, 2001; Morrison et al, 2000; Saint-Cyr et al, 2000), attention (Alegret et al, 2001), and in forming spatial and conditional associations (Alegret et al, 2001). However, with the exception of deficits in phonemic and semantic verbal fluency, which have been found to persist in long term follow up, the majority of the other cognitive deficits are short-lived and not observed in the long-term (Funkiewiez et al, 2006). Post-operatively, significant differences in specific aspects of cognition, namely verbal fluency, response selection under competition on the Stroop test and conditional associative learning have been reported with the stimulators on versus off (Jahanshahi et al, 2000; Pilon et al, 2000).

1.4.2 Mood

Reports of the affective outcome of STN DBS have been mixed, with some authors finding significant improvement in depression and anxiety after STN DBS (Krack et al,

2001), and others reporting worsening of mood following surgery (Funkiewiez et al, 2004; Stefurak et al, 2003). Compared to pre-surgical levels, self-reported depression and anxiety can be improved post-operatively (Castelli et al, 2006). This may simply reflect the reactive elevation of mood associated with improved motor function and the associated reduction of disability. In addition, a host of stimulation-induced behavioural and affective changes have been documented in reports. These have included acute depression and suicide (Funkiewiez et al, 2004; Stefurak et al, 2003), manic episodes (Funkiewiez et al, 2004), visual hallucinations (Krack et al, 2003), apathy (Funkiewiez et al, 2004; Krack et al, 2003), pseudobulbar crying (Okun et al, 2004), aggressive behaviour (Funkiewiez et al, 2004; Krack et al, 2003), and impaired processing of emotional facial expressions (Dujardin et al, 2004). While some of these affective responses may reflect amplification of pre-existing psychiatric problems (Houeto et al, 2002), others such as apathy, mania and aggressive behaviour have been mainly limited to the immediate post-surgical phase when stimulation has just been introduced and disappear over time (Krack et al, 2003).

In contrast, a number of studies have shown that stimulation of some electrode contacts result in acute alteration of affective state. Krack et al (2001) reported a patient whose depression and suicidal thoughts were alleviated with stimulation post surgery, however upon increasing stimulation this improved mood would culminate in fitful bursts of laughter that became problematic. They reported another patient whose mildly depressed mood and frustration was improved post-operatively; however upon chronic stimulation he became labile, laughing and crying more readily than normal with exposure to appropriate stimuli (Krack et al, 2001). This change persisted for the duration of

stimulation. However, in a female patient, an increased depressive state with feelings of profound sadness, emptiness, fatigue, guilt and thoughts of death was found by Bejjani et al (1999), which persisted for the duration of stimulation. In a number of cases, adverse acute affective effects were observed when stimulating through contacts that were not in the STN (eg Bejjani et al, 1998). However, in most cases, behavioural effects are documented with electrodes accurately placed in the sensorimotor STN. It is apparent, therefore, that STN DBS can influence affective states in PD.

1.4.3 Social adjustment

In their study of patients with PD who underwent STN DBS surgery Schupbach et al (2005) found that although patients experienced motor improvement, showed no adverse effects on cognition, and reported improvement in quality of life and activities of daily living, social adjustment did not improve. This resulted in patients reporting difficulties in their relationships with their spouses and families and in their social interaction. Furthermore, a number of patients who were employed prior to surgery were unwilling to go back to work, despite improvement of their Parkinson's disease and reduction of disability (Schupbach et al, 2005).

Therefore, due to the numerous potential non-motor outcomes of STN DBS surgery appropriate selection of patients is essential. This highlights the importance of neuropsychological assessment in the selection of suitable candidates for this surgery, as some patients, such as those with dementia, cannot benefit from surgery (Saint-Cyr & Trepanier, 2000).

Therefore, it is apparent that as well as providing relief of motor symptoms through its actions on motor areas, DBS also affects non-motor functions, including affective, cognitive and psychosocial functioning. In the remainder of this review, the existing literature on apathy in PD and apathy in patients with PD who have undergone STN DBS will be discussed and critically appraised.

What factors influence the development of apathy in PD?

1.5 Apathy in Parkinson's disease

Apathy is a disorder that presents with behavioural, emotional and motivational features, including reduced interest and participation in purposeful behaviours, lack of initiative, affective flattening and indifference (Pluck & Brown, 2002), and is associated with a variety of negative outcomes (Roth, Flashman & McAllister, 2007). Marin's (1991) definition of apathy is a primary loss of motivation in the absence of emotional distress, intellectual impairment or clouding of consciousness. The "negative symptoms" of apathy that can occur in various psychiatric and neurological disorders in the domains of cognition, emotion and behaviour, which can represent both a symptom and a syndrome signifying a loss of motivation, have been emphasised (Marin, 1991). Levy and Czernecki (2006) have defined apathy as the quantitative reduction of self-generated and purposeful behaviours that can, therefore, be understood as a pathology of goal-directed behaviour resulting from disruption of the basal ganglia and related circuits. They proposed the existence of three subtypes of apathy, namely apathy of cognition, emotion and auto-activation, each relating to a specific type of frontal-subcortical dysfunction, reflecting the disintegration of motivational, emotional and cognitive processes (Levy & Czernecki, 2006).

Apathy in PD has been found to present as an isolated lack of motivation without anhedonia, hopelessness and low mood, which differs from the presentation of apathy in depression (Ferreri, Agboku & Gauthier, 2006). Rates of apathy in patients with PD vary, with some authors reporting rates between 12% (Starkstein et al, 1992) and 45% (Isella et al, 2002). This discrepancy may be due to reliance on divergent diagnostic criteria, assessment of different PD samples such as community versus hospital based samples or may reflect the lack of a validated, standardised instrument for detecting the presence and severity of apathy in this population (ibid). Some authors have suggested that apathy is a core feature of PD, as significantly higher levels of apathy have been found in PD patients than in matched controls with other neurological disorders, for example Dystonia (Kirsch-Darrow, Fernandez, Marsiske, Okun & Bowers, 2006). The factors influencing the development of apathy in Parkinson's disease will be discussed below. Table 1 details these influencing factors.

1.5.1 Apathy and Dopamine

The deficiency of the neurotransmitter dopamine is the hallmark of PD (Brown & Jahanshahi, 1991). However, dopamine is also involved in reward and motivation (Dujardin et al, 2007). It has been proposed that dopamine deficiency underlies a number of disorders that cause apathy (Marin, 1991). Lack of motivation is an important element of apathy (Pluck & Brown, 2002), which some authors have stated is the cardinal feature of apathy in PD (Ferreri et al, 2006). However, Czernecki, Pillion, Houeto, Pochon, Levy and Dubois (2002) found that the severity of apathy in PD patients differed significantly between "on" and "off" Levodopa states. They and other authors have suggested that apathy may be at least partially dopamine dependent and

that dopaminergic medication may be helpful for the treatment of apathy (Czernecki et al, 2002; Roth et al, 2007), although this has been disputed by some authors (Brown & Pluck, 2000). Dopamine deficiency may, therefore, at least partly account for the high prevalence of apathy in PD.

1.5.2 Apathy and motor symptoms of PD

Pluck & Brown (2002) in their comparative study of apathy in PD and equally disabled patients with osteoarthritis found that significant levels of apathy only occurred in the PD sample. On this basis they suggested that apathy is a true feature of PD and a direct consequence of the disease, rather than a psychological reaction to physical deterioration or adjustment to disability (Pluck & Brown, 2002). In accordance with this finding Dujardin et al, (2007) found no association between motor symptom severity and apathy in their study, implying that apathy is not a reaction to motor deterioration, but part and parcel of the disease process.

1.5.3 Apathy, the basal ganglia and frontal lobe dysfunction

In an analysis of the literature on basal ganglia lesions it was found that Abulia (apathy with loss of initiative, spontaneous thought and emotional responses) was the most common behavioural disorder arising from lesions in this area (Bhatia & Marsden, 1994). Levy & Czernecki (2006) hypothesised that apathy occurring in PD may be the emotional subtype, due to dysfunction of the orbito-medial-PFC-ventral striatum circuit. This emphasises the role of the frontal-subcortical circuits in both apathy and PD. However, they also offer an alternative hypothesis for the occurrence of apathy in PD, as

presenting as the cognitive subtype, resulting from disruption in cognitive executive processing leading to deficits in planning and organization of goal-directed behaviours.

Apathy has been related to frontal lobe dysfunction as it often occurs following damage to the frontal lobes or related structures, such as the basal ganglia (Dujardin et al, 2007). As apathy is commonly seen in patients with basal ganglia disorders the involvement of the frontal-subcortical circuits have been suggested in the development of apathy. Clear associations between apathy and executive dysfunction have been reported by many authors including Pluck & Brown (2002), Isella et al (2002) and Starkstein et al (1992), who found that apathetic PD patients perform worse on tests of executive function such as the Controlled Oral Word Association test and Trail making test B. On tasks of executive function PD patients have been found to perform worse than healthy controls (Pluck & Brown, 2002). This supports the hypothesis that the frontal-subcortical circuits are involved in both apathy and PD.

1.5.4 Apathy and Depression

Although apathy and depression often co-exist in PD, some authors have found that despite this correlation, the presence of one disorder did not predict the presence of the other (Pluck & Brown, 2002; Sockeel et al, 2006). However, it has been found that, if present, the severity of depressive symptoms contributes to the overall severity of apathy (Dujardin, 2007). Isella et al (2002) found no correlation between apathy and depression in their sample of thirty PD patients, 33% of whom were apathetic in the absence of depression and 44.4% were depressed in the absence of apathy.

Levy et al (1998), in their study, of 154 patients with neurological disorders also found no correlation between apathy and depression. However, this study did not focus specifically on PD, and they found that few PD patients presented with apathy alone (n = 2; 5%), compared with depression (n = 11; 28%) or depression plus apathy (n = 11; 28%). The importance of increasing our understanding of apathy in PD and distinguishing depression and apathy in this group has been highlighted (Kirsch-Darrow et al, 2006). This is especially important when considering the negative outcomes with which apathy is associated and the potential necessity for treatment with both pharmacologic and psychological treatments (Roth et al, 2007).

1.5.5 Apathy and Cognitive impairment/ Dementia

Dementia occurs in approximately 30% of patients with PD (Anderson, 2004) and has been positively correlated with the presence of apathy in PD, (Brown & Pluck, 2000). Dujardin et al (2007) found that apathy profiles vary according to the clinical presentation of PD, finding relatively few cognitively stable patients and a modest number of patients with cognitive fluctuation were apathetic. They found, however, that PD patients with dementia were more likely to suffer apathy and that cognitive impairment was the main factor contributing to the worsening of apathy (Dujardin et al, 2007). This, therefore, suggests an association between cognitive impairment and apathy in PD. Levy et al (1998) also found an association between apathy and cognitive impairment in PD and Alzheimer's disease populations.

Pluck and Brown (2002) found that, although patients with dementia made up only a small proportion of their sample, all of them were defined as apathetic. They suggested,

on this basis, these patients may be in the extreme range of dysfunction or may represent a subgroup of PD patients, with marked apathy and cognitive dysfunction, which are the hallmarks of classic fronto-subcortical dementia. However, in contrast, other authors including Isella et al (2002) and Starkstein et al (1998) found no relationship between performance on global cognitive tests or specific memory tests and apathy and therefore concluded that there is no relationship between apathy and cognitive impairment in PD.

1.5.6 Apathy and other psychiatric sequelae in PD

Drugs used to treat PD, such as levodopa, can have adverse neuropsychiatric effects, most prominently psychosis and delirium (Young, Camicioli & Ganzini, 1997). Santangelo et al (2007) found that patients who experienced hallucinations had higher apathy scores than those who had not experienced hallucinations. However, the nature of apathy and the behavioural manifestation of the disorder seem at odds with some other psychiatric disorders, such as the hypervigilance of anxiety (Pluck & Brown, 2002).

Table 1(a). Factors associated with the occurrence of apathy in PD

<i>Study</i>	<i>Cognitive impairment</i>	<i>Depression</i>	<i>Executive dysfunction</i>	<i>Other psychiatric sequelae</i>	<i>Motor symptoms</i>	<i>Dementia</i>
<i>Pluck & Brown (2002)</i>	∅	X	∅	X	X	∅
<i>Dujardin et al (2007)</i>	∅				X	∅
<i>Funkewiez et al (2006)</i>			∅			
<i>Santangelo et al (2007)</i>				∅		
<i>Levy et al (1998)</i>		X				∅
<i>Isella et al (2002)</i>	X	X	∅			X
<i>Starkstein et al (1998)</i>	X		∅			X

Legend:

x = Not associated with the occurrence of apathy in PD.

∅ = Associated with the occurrence of apathy in PD.

Table 1(a) illustrates some of the main findings of the aforementioned studies. It is apparent that although the factors influencing the occurrence of apathy in PD are controversial, there are a number of potential risk factors which increase the likelihood of apathy in this population. The main risk factors are the presence of dementia and executive dysfunction. The presence of depression, severity of motor symptoms and other psychiatric sequelae have been found to not influence the occurrence of apathy in PD. However, conflicting results have been found regarding the influence of cognitive impairment on apathy in PD. This may be due to differing inclusion criteria, differing definitions of impairment and incongruent samples used in different studies.

What influence, if any, does STN DBS have on apathy?

1.6 Apathy and STN DBS surgery

The question of whether DBS of the STN in Parkinson's disease influences apathy is a controversial one, and has wide ranging implications for treatment of patients with PD. The investigation of apathy after STN DBS surgery is important as although patients may obtain great motor benefit from surgery, if there is a risk of increased or newly induced apathy, this could have significant implications; initially for the selection of candidates for surgical treatment and subsequently for patients quality of life and carer burden. If apathy is found to be a common occurrence following DBS of the STN, this may influence the patients and families decisions about whether or not to have surgery.

1.6.1 Occurrence of apathy after STN DBS

Some authors have concluded that STN stimulation may induce apathy or that apathy may worsen after such surgery. Studies have shown that apathy worsens in comparison

to preoperative assessment after STN DBS surgery at three months and six months postoperatively in the absence of depression or worsening of existing anxiety levels (Drapier et al, 2005). Saint-Cyr et al (2000) also found increased reports of apathy as assessed by carer responses on the Frontal Lobe Personality Scale by carers at 9 – 12 months post-surgery, suggesting worsening of apathy. A study comparing the neuropsychological outcomes of PD patients who underwent either pallidotomy (lesioning of the GPi) or STN DBS found that post-operative frontal lobe behavioural changes occurred in both groups (Trepanier et al, 2000).

Temel et al (2006) in their systematic review of behavioural changes after bilateral STN stimulation in advanced PD found that apathy was reported in <0.5% (n = 7) of the 1398 patients included in their selected studies. They did however note that although rates of apathy were low, when it occurred apathy was often chronic and had substantial effects on the patients and their families (Temel et al, 2006). A three-year long term follow-up study of seventy-seven patients also found newly occurring cases of apathy and worsening of pre-existing apathy, with overall group rates rising from 8.7% pre-operatively to 24.6% post-operatively (Funkiewiez et al, 2004).

Although it has been reported that acute effects of stimulation initially result in improvement in motivation, apathy has been found to worsen after chronic stimulation (3 months post surgery) in the same patient group (Funkiewiez et al 2006). In this study of twenty-two patients, new cases of apathy were found in four patients, and an existing pre-operative case of apathy persisted after surgery (Funkiewiez et al, 2006). Not all of the new cases in this study were above cut-off point for diagnosis of clinical apathy;

however the occurrence of apathy in these patients was sufficiently significant to be reported as problematic by patients and families, thus highlighting the difficulty encountered by patients experiencing apathy and the carer burden resulting from it.

Schupbach et al (2005), in their 5-year follow-up study of STN DBS found newly occurring cases of apathy, half of whom were transient ($n = 4$) and the other half permanent ($n = 4$). The authors noted that the apathetic patients' activities of daily living (ADL) had returned to baseline pre-operative levels at 24 months after surgery. They concluded that this reduction in ADL may have occurred due to the adverse effects of apathy (Schupbach et al, 2005).

1.6.2 Improvement/ no change in apathy after STN DBS

Castelli et al (2006) found apathy to be stable preoperatively and 15 months after STN DBS surgery. Contarino et al (2006), in their 5-year follow-up study of STN DBS in PD, found that one of the eleven patients studied developed apathy. The authors concluded that the surgery had a low cognitive and behavioural morbidity rate and was, a safe procedure, however, this study did not include a non-operated control group for comparison of neuropsychological and behavioural outcome of surgery. Other investigators have found that STN stimulation can in fact improve apathy (Czernecki, et al, 2006). This study has been criticised, however, as the results were obtained by comparison of presence of apathy under "on-stimulation" versus "off stimulation" conditions, which is not an appropriate assessment procedure for apathy, as it is unlikely to be state dependent. It should also be noted that in their sample of 23 patients, the

authors reported improvement in apathy in nine patients, no significant change in eight patients and aggravation of apathy in one patient (Czernicki et al, 2005).

1.6.3 Differences among those who develop apathy post-op and those who do not

Czernicki et al (2005) highlighted the importance of appropriate pre-operative patient selection, according to specific criteria, as they found that younger patients with moderate disease duration and severity did not develop apathy post-operatively. Other authors, have suggested that older patients may be more likely to develop adverse effects from STN DBS surgery, such as apathy and difficulties in executive functioning, as their neural networks may not be as flexible as younger patients (Jahanshahi, et al 2000). Apathy and age at surgery were found to be correlated, in the absence of a relationship between cognitive outcome and age in a study of the influence of aging on outcome in STN DBS surgery at two-year post-operative follow up (Ory-Magne et al, 2007). A correlation was also found between depression and aging in this study; where older patients were more likely to become apathetic or depressed post-operatively (Ory-Magne et al, 2007).

1.7 Apathy, Parkinson's disease and the Frontal-subcortical circuits

As aforementioned, Alexander et al (1986) identified the five frontal-subcortical circuits, connecting the frontal lobes and striatum, limbic and thalamic structures. Among the circuits they identified was the Anterior Cingulate Circuit (ACC), which Cummings (1993) suggested was involved in apathy. This circuit was found to be important in motivational mechanisms (Bonelli & Cummings, 2007). Apathy is a prominent feature of disorders associated with lesions to this circuit, e.g. akinetic mutism and abulia.

Evidence from animal studies highlights the role of dopamine in this circuit as, behavioural deficits occurring as a result of an induced state of akinetic mutism could be reversed by administration of dopamine agonists (ibid). Dujardin et al (2007) suggested that the high prevalence of apathy in PD confirms the involvement of the frontal-subcortical circuits.

Evidence from clinical-pathology and functional neuroimaging suggests that the frontal-subcortical pathways mediate executive dysfunction and apathy in degenerative neurological disorders, including PD (Kuzis, Sabe, & Tiberti, 1999). Therefore, the disruption of the frontal-subcortical connections, may underlie the pathogenesis or co-occurrence of apathy, executive dysfunction and Parkinsonian signs (Alexander & Crutcher, 1990).

1.8 Outcome of apathy in PD

It is apparent, therefore, that a number of factors influence the development of apathy in patients with PD. Some of these factors are controversial, as contradictory evidence exists for their involvement in or association with apathy in PD. There are many reasons for this contradictory evidence, including different methods of data collection, namely tools for identifying and diagnosing apathy and differing age groups and prior psychiatric profiles of the patients included. With reference to apathy in patients who have undergone STN DBS surgery for the amelioration of their PD symptoms, it must be acknowledged that surgery of this kind is still in relative infancy, and more research must be done to assess its long-term effects.

Despite this, the fact remains that apathy is prevalent in PD, both in patients who receive pharmacological treatment and patients who receive surgical treatment with DBS of the STN. Therefore the clinical and real life implications of apathy must be considered. It has been reported by many authors that when apathy occurs in patients with PD it is consistently reported by patients and caregivers as a concern, even if the apathy is below clinical levels of significance. This may be due to the negative influence of apathy on quality of life and activities of daily living (Pluck & Brown, 2002).

1.9 Treatment of Apathy in patients with Parkinson's disease

1.9.1 Pharmacological and surgical treatment

It has been reported that apathy appears to respond to dopamine agonists (Roth et al, 2007). However, apathy in patients with PD may also respond to cholinesterase inhibitors (Lauterbach, 2005), which have been found to reduce apathy in patients with dementia and traumatic brain injury (Roth et al, 2007). However, clinical benefits of pharmacological treatment of apathy in PD, including dopamine agonists or methylphenidate are reported to be disappointing and limited by side-effects (Ferreri, et al, 2006). Some authors have found acute improvement in apathy after STN DBS (Czernecki et al, 2005), however the long term implications of surgical intervention and long term high frequency stimulation on apathy need further assessment as the evidence is contradictory.

1.9.2 Psychological Intervention

Ferreri et al (2006) have found that “psycho-education” of patients and caregivers helps them to distinguish apathy symptoms from depression and laziness. They recommend coaching and prompting to help decrease the difficulties of executive dysfunction and planning, and greater control of Parkinson’s symptoms to help alleviate apathy (Ferreri et al, 2006). Further study is required to determine the efficacy of additional psychological approaches for patients with PD who experience apathy.

1.10 Conclusions

The factors influencing the occurrence and development of apathy in PD are controversial, however, it appears that damage to the basal ganglia or frontal lobes, psychiatric phenomena, namely hallucinations and dementia are risk factors for apathy in patients with PD, as it appears that higher rates of apathy occur in PD patients who experience these difficulties. Factors that do not appear to influence apathy in this patient group are motor symptom severity and presence of depression. However, although depression does not predict the occurrence of apathy in PD, the presence of depressive symptoms increases the severity of apathy.

Dopamine deficiency may potentially account for the prevalence of apathy in PD, as apathy in PD appears to be at least in part dopamine-dependant, (Czernecki et al, 2008; Czernecki et al, 2002). However, non-dopaminergic circuits have also been implicated in the development of apathy in PD, as a link has been found between apathy and cognitive impairment in patients with PD (Dujardin et al 2007; Pluck & Brown, 2002).

The influence of STN DBS and other surgical interventions for the treatment of PD on apathy is unclear, with studies finding conflicting results. Therefore further investigation of apathy in post-operative patients is required. However, despite conflicting findings, it appears that certain risk factors may exist that mean specific PD patients are at higher risk of developing apathy post-operatively. These risk factors are increased age, longer pre-operative disease duration, and a higher UPDRS score, indicating worse motor symptom severity.

STN DBS in PD is a relatively new surgical procedure, having been developed initially only twenty years ago (Benabid, 2007). It is impossible, at this stage, to determine the longer-term effects of this surgery, however due to the negative effects of apathy for both patients and caregivers the need for continued study of apathy in post-operative patients is highlighted. This is important so as to identify the potential risks of apathy after surgery and potential prognostic indicators for this, which the patients would need to weigh against the great motor benefit that they could experience.

1.11 Clinical implications and future directions

1.11.1 STN DBS Patient selection

These findings highlight the need for thorough neuropsychological assessment of both the cognitive and affective domains in all patients with PD who are candidates for STN DBS surgery. However, as some studies have found that apathy can occur in patients with no prior history of the disorder the importance of informing patients and families of risk of developing apathy after surgery is also highlighted. This would allow them to make informed decisions regarding undertaking surgery for the alleviation of motor

symptoms, which may result in affective side effects known to cause distress and negative outcomes for both patients and families. In the light of the findings of the aforementioned studies these risk and benefits must be weighed up with respect to candidate selection by clinicians on one hand and informed consent of patients considered for surgery on the other.

1.11.2 Role of psychology in the assessment and treatment of apathy in PD

Therefore, it is apparent that numerous factors may influence the development of apathy in patients with PD. The prevalence of apathy in PD is high and the consequences of apathy in this group are negative for both the patient and their caregivers. At the clinical level, psychology services, therefore, have an important role to play in the assessment and treatment of patients with PD who develop apathy and in the support of their families and caregivers. On a research level, psychologists must also continue to study apathy in PD and evaluate the interventions that can be provided to reduce its negative effects on patients and their broader life contexts.

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Part 2. Empirical Paper

“The impact of Deep Brain Stimulation of the Subthalamic nucleus on reward responsiveness in patients with Parkinson’s disease”

Abstract

Parkinson's disease (PD) results from the degeneration of dopamine-producing cells in the striatum, leading to excessive inhibition of frontal areas and the motor symptoms of PD. Deep brain stimulation (DBS) of the Subthalamic Nucleus (STN) is an effective treatment for PD motor symptoms. This study aimed to investigate the effect of STN DBS on reward responsiveness, assessed by performance on a 'reaction time and reward' paradigm and a card-sorting task in both "on" and "off" stimulation conditions. Matched healthy controls performed the reaction time paradigm and card-sorting task twice. Hypothesis one proposed that STN DBS would speed up initiation and movement times for patients in the "on" stimulation condition as compared with the "off" stimulation condition. This was supported of movement time, and a trend towards significance was found for improvement in initiation time. Hypothesis two proposed that the presence of reward would speed up initiation times in patients and controls. This was supported. Hypothesis three proposed that STN DBS would improve patients initiation time in response to reward conditions to a greater extent than repetition would improve controls initiation time. This was not supported. Hypothesis four proposed that STN DBS would improve patients performance on the CARROT card sorting task in response to reward conditions to a greater extent than repetition would improve controls performance on this task. This was not supported. Hypothesis five stated that the presence of a warning signal would improve patients initiation time. this was supported. Hypothesis five proposed that the presence of a warning signal would significantly improve patients initiation time. This was supported. The results are discussed with reference to the effects of STN DBS on response time, reward responsiveness and the proposed neural circuits mediating motivation and the limitations of the current study.

Introduction

2.0 Parkinson's disease

Parkinson's disease (PD) is a movement disorder arising from the death of striatal dopaminergic neurons and subsequent deficiency of dopamine, resulting in the excessive inhibition of cortical motor areas, which leads to the characteristic symptoms of bradykinesia (slowness of movement) and akinesia (poverty of movement) (Crossman & Neary, 2000). In PD the balance of activity in the frontal-subcortical pathways are affected (Alexander De Long & Strick, 1986).

The level of deficiency in PD appears to be at the translation of intention into action, as patients with PD know what they want to do but cannot translate this into activity (Frith, 1992). This hypothesis is supported by the phenomenon of “kinesia paradoxa”, or paradoxical kinesis, where PD patients have been known to move suddenly and quickly in response to urgent external stimuli, eg: in response to a dangerous situation (Ballanger et al, 2006; Niv & Rivlin-Etzion, 2007). The fact that external cues can help PD patients improve their performance on experimental movement tasks, such as preventing a ball dropping by pressing a switch (Ballanger et al, 2006) and in real world situations, such as the provision of lines on the floor where a patient is required to walk (Jahanshahi & Frith, 1998) also supports this hypothesis. Therefore, PD could be considered a disorder of willed action.

2.0.1 Reaction time studies

One way of experimentally assessing movement deficits in PD is through reaction time studies, which usually take the form of manual tasks requiring the patient to move as

quickly as possible from one response button to another. Two reaction times are differentiated in this paradigm, namely initiation time, which is estimated as the time it takes for the participant to lift his/her finger from the response key upon presentation of the imperative stimulus and movement time, which is estimated as the time it takes between the participant lifting his/her finger from the response key and pressing the target key upon presentation of the imperative stimulus.

Reaction time studies can tell us more about PD symptoms as they allow the differentiation between cognitive and motor impairments of the disease (Kutukcu, Marks, Goodwin & Aminoff, 1999). Reaction time paradigms enable this dissociation as initiation time, which is associated with cognition, namely motor planning and motivational processes, and movement time, which is associated with motor function, can be assessed individually on these tasks (Temel et al, 2006). Therefore, reaction time studies in PD can yield valuable information about the symptoms of the disease and the neural systems that underlie these deficits.

Simple reaction time (SRT) studies, where participants make the same response to the same stimulus over trials have found that reaction times are impaired in patients with PD compared with healthy controls (de Frias, Dixon, Fisher & Camicioli, 2007; Kutukcu et al, 1999; Mazzucchi et al, 1993), and show a greater intraindividual variability of response than healthy controls (de Frias et al, 2007; Erbmeier et al, 1992). Patients with PD have deficits in both initiation times (Evarts, Teravainen & Calne, 1981) and movement time (Erbmeier et al, 1992) relative to age-matched controls.

Advanced warning cues are sometimes used in reaction time studies to investigate the effects of warning on initiation and movement time. These warning cues precede the imperative stimulus and therefore warn the participant of the imminent occurrence of the stimulus. Studies looking at the effects of warning cues on reaction time in PD suggest that PD patients benefit from advance warning signal in speeding reaction time (Jahanshahi, Brown & Marsden, 1992). Jahanshahi, Brown and Marsden (1993) found that PD patients are more dependent on warning to improve their performance on SRT tasks in comparison to patients with Huntington's disease or cerebellar disease, and concluded that PD patients selectively require this external stimulus to maintain motor readiness.

2.1 Reaction time in patients with PD who have undergone STN DBS surgery

The Subthalamic Nucleus (STN) is a subcortical structure, with both somatomotor, limbic and cognitive functions, which forms part of the basal ganglia (Crosman & Neary, 2000). In PD there is excessive excitatory drive from the STN (Alexander et al, 1986). As dopamine replacement drug therapy has time-limited effects; giving relief of symptoms for approximately five years, after which hard-to-control motor fluctuations develop, STN Deep brain stimulation (DBS) is a neurosurgical treatment option for the reduction of symptoms of PD using high frequency stimulation (HFS) of the STN (Limousin, et al 1998). It has been proposed that the improvement of motor symptoms results from the direct inhibition of STN over-activity and by influencing the motor frontal-subcortical circuit (Czernecki et al 2005), which is one of a group of five parallel, segregated functional circuits that link specific areas of the basal ganglia with discrete areas of the frontal cortex (Bonnelli & Cummings, 2007; Cummings, 1993). The

motor, cognitive, affective and motivational functions of the striatum are mediated through the direct and indirect pathways of these circuits (Alexander et al, 1986).

Reaction time studies of patients who have undergone STN DBS can further inform us about the functions of the STN in PD and its influence on both the motor circuitry and the other frontal-subcortical circuits involved in affect and motivation (Alexander et al, 1986). Evidence suggests that STN DBS affects the Anterior Cingulate Circuit (ACC), which mediates motivated behaviour (Czernecki et al, 2005). Studies have found that initiation and movement times in patients who have undergone DBS for the treatment of PD are significantly improved in the “on” stimulation state (Ellrichmann, Harati and Muller, 2008; Kumru et al 2004), however response times within this group remain slower than healthy controls (Temel et al 2006).

However, one area which to date has received little attention in PD and healthy populations is motivational influence on initiation and movement speed. Healthy people can improve the speed of motor performance when motivated for example writing faster during an exam or walking faster when in a hurry to avoid being late. Therefore, motivation can influence motor speed.

2.1.1 The Role of Dopamine in Reaction time deficits in PD

Gauntlett-Gilbert & Brown (1998) suggest that dopamine deficiency is a factor underlying reaction time deficits seen in PD, as these deficits are rectified by the administration of dopamine replacement therapy, where slower reaction times, which require less dopamine recover before faster reaction times. Lalonde and Botez-Marquard

(1997) found that both simple and choice reaction times are susceptible to modulation by brain dopamine levels; however they also raise the issue that other non-dopaminergic neurons contribute to sensorimotor slowing in PD (Lalonde & Botez-Marquard, 1997). However, Jahanshahi et al (1992) found that reaction times in PD were not dopamine dependent, suggesting that RT slowness may be a non-specific index of brain dysfunction present in other disorders such as Huntington's disease, cerebellar disease (Jahanshahi et al, 1993) or dystonia (Jahanshahi et al, 2001) rather than representing dopamine deficiency.

2.2 Dopamine, Reward and Motivation

2.2.1 Dopamine and Reward

Reward, which can be monetary or some other desired object, acts as a positive reinforcer in goal directed behaviour, as objects signalling reward are labelled with positive motivational value, which increases the likelihood of engaging in specific behaviours that will lead to obtaining that reward (Martin-Soelach et al, 2001). Studies of reward related behaviour suggest that the striatum and related areas of the brain are involved in the processing of reward related information (Nieoullon & Coquerel, 2003).

Dopamine depletion is accepted as the causal process in Parkinson's disease. In addition to motor control, dopamine neurotransmission also has other functions in the brain; it has effects on motivation, reward-related information processing and behaviour (Berridge & Robinson 2003; Tricomi et al 2004) and has been implicated in the detection of novelty (Nieoullon & Coquerel, 2003). Arias-Carrion and Poppel (2007)

state that reward anticipation or omission results in changes in the activity of dopaminergic neurons, suggesting a role for this neurotransmitter in motivation

Disorders of motivation, specifically apathy, are reported to occur in PD (Isella et al, 2002). Rates of apathy in patients with PD vary, with some authors reporting rates between 16 and 42% (Sockeel et al, 2006). Lack of motivation is an important element of apathy (Pluck & Brown, 2002), which some authors have stated is the cardinal feature of apathy in PD and differentiates it from the presentation of apathy in depression (Ferrerri, Agboku & Gauthier, 2006). Therefore, not only does dopamine have motor functions within the brain, but it also influences motivation.

2.2.2 The modulation of reaction times by monetary incentive

Czernecki et al (2002), in their study of motivation and reward in PD found patients treated with dopaminergic medication in the “off” medication condition had lower motivation and had impaired sensitivity-to-reward flexibility. In the “on” medication state they found PD patients had improved motivation (Czernecki et al, 2002). From these findings the authors concluded that the limbic frontal-subcortical circuits, which are dysfunctional in PD, were implicated in motivation.

Reward responsiveness refers to the modulation of a specific behaviour by the presence of a reward. In a study comparing effects of basal ganglia damage on reward responsiveness Schmidt et al (2008) found that, in response to a monetary incentive, PD patients “off” dopaminergic medication were able to modulate their grip-force in response to reward, although at a lower rate than controls. The authors suggested that

such functional preservation may occur due to spared dopaminergic innervation of the limbic circuits passing from orbital and medial prefrontal cortices through the basal ganglia (ibid).

The study of Mir et al (In press) focused on the effect of monetary reward on reaction times of healthy participants. They found that monetary incentive significantly speeded up initiation time in reaction time tasks. Therefore it appears that monetary reward was an incentive to speed up initiation of movement in these tasks. As initiation time was more significantly affected than movement time the authors concluded that the main effect of monetary incentive was on the pre-movement processes rather than on the execution of the movement (Mir et al, In press).

2.3 Summary

Parkinson's disease represents a disorder characterized by dopamine deficiency, which can be considered to be a disorder of willed action, manifested by slowed movements and a reduction in spontaneous movement. Reaction time studies have found that PD patients have slower simple reaction times than controls. However, external cues can help patients with PD to improve motor performance. Studies using financial reward have found that reward can act as an incentive for healthy participants to improve reaction times. Dopamine is a neurotransmitter with both motor and motivational consequences and is deficient in PD. Treatments for PD include dopaminergic medication and neurosurgical techniques, including STN DBS, which it has been suggested, alleviates PD symptoms by operating as a functional lesion. Schmidt et al (2008) found that patients with basal ganglia lesions fail to distinguish between

monetary incentives. Therefore, in light of the dopamine deficiency in PD and the mechanism of STN DBS treatment, it is of interest whether patients are capable of speeding up their reaction times in anticipation of monetary reward in a similar manner to healthy controls.

2.4 Aim

The aim of this study was to investigate the effect of DBS of the STN on processes of response initiation and execution, and reward responsiveness in patients with PD in unrewarded conditions compared to two rewarded conditions where patients were instructed to speed up their reaction times in anticipation of incremental monetary incentive, on a computerised task and on a manual card-sorting task. The performance of the patients with DBS “on” versus “off” was compared to matched controls who performed the same tasks and conditions twice, to control for practice effects.

Based on the existing evidence in relation to STN DBS, reaction times and reward, the following hypotheses were formulated:

- (1) STN DBS would speed up initiation time and movement time for patients in the “on” stimulation condition as compared with the “off” stimulation condition.
- (2) The presence of reward would speed up initiation time in patients and controls.
- (3) STN DBS would improve patients initiation time in response to reward conditions to a greater extent than repetition would improve controls initiation time in response to reward
- (4) STN DBS would improve patients performance on the CARROT card-sorting task in response to reward conditions to a greater extent than repetition would improve controls performance on this task in response to reward.

(5) The presence of a warning signal would improve patients initiation time.

Method

In order to test these hypotheses, 12 patients with Parkinson's disease (PD) who had undergone Deep Brain Stimulation (DBS) surgery of the Subthalamic Nucleus (STN) for the treatment of their motor symptoms and 11 age-matched controls were assessed on a computerised reaction time task and a card sorting task in order to determine reward responsiveness. A range of cognitive, mood and personality measures were also used to compare the relationship of reward responsiveness in DBS patients and controls on these variables.

2.5 Research design

A mixed between groups (PD patients vs controls) and within subjects design (DBS on vs off for the patients or time 1 vs time 2 assessment for controls) was used.

2.6 Power Analysis

The following power calculation was used to determine the sample size necessary to obtain sufficient power significant effects; $[sd^2 / (\mu_2 - \mu_1)^2 \times 10.5]$. On the basis of this calculation a sample size of 16 was determined to be necessary. On the basis of time limitations, patient availability and inclusion criteria 12 patients were included in the study and 10 successfully completed the protocol. Therefore the current study is underpowered. However, as the population is extremely small and the protocol for this study necessitated a long period off stimulation and medication, the prospect of finding

difficulty obtaining a sample size of 16 was considered. Therefore, sample sizes from published articles on DBS using similar protocols were also investigated and it was found that other authors used similarly small sample sizes; namely Mir et al (in press) (n = 16); Mazzoni et al (2007) (n = 7); and Ballanger et al (2006) (n = 6). Therefore, although this study is underpowered and this is an obvious limitation for the interpretation of results, the sample obtained was considered sufficient in the context of the population and time limitations for the purposes of this research.

2.7 Participants

2.7.1 Patients

The PD patients were all current patients at the National Hospital for Neurology and Neurosurgery in Queen Square, London, who had undergone DBS surgery in the Functional Neurosurgery Unit performed by the same surgical team, (M. Hariz, K. Ashkan, L. Zrinizo). The patients were identified from existing clinical lists and potential candidates were recommended by the Consultant Neuropsychologist (M. Jahanshahi) and post-doctoral research fellow (L. Wilkinson), both specialising in the study and clinical assessment of movement disorders.

Patients were selected on the basis of having undergone bilateral STN DBS surgery at least six months prior to entering the study. Patients with known psychiatric history or cognitive impairment were excluded. Only surgical patients with a good response to DBS, substantial improvement of clinical symptoms and post-surgery MRI evidence of correct positioning of the electrodes were included. Patients were also selected on the basis of being willing to remain off stimulation for approximately forty-five minutes,

while also off medication. Thirteen PD patients were identified as potential participants and approached to participate in the study; one patient refused due to extreme motor difficulty experienced when off stimulation. Twelve patients agreed to participate; two patients were unable to successfully complete the study due to extreme motor difficulty during the off stimulation state, namely dystonic cramps and pain. Therefore, 10 patients successfully completed the study. Patients were tested off dopaminergic medication, after overnight withdrawal of medication for an average of 15 hours (SD = 3 hours, range 11 to 20 hours). Demographic and clinical characteristics of the patients are presented below in Table 2 (a).

Table 2(a). Demographic and clinical characteristics of the patients with Parkinson's disease

Neurological characteristics	Mean (SD)	Range
<i>Age at onset (years)</i>	<i>43(7)</i>	<i>39 – 78</i>
<i>Duration of disease (years)</i>	<i>14(5)</i>	<i>8 – 24</i>
<i>UPDRS “off” stimulation score</i>	<i>42(16)</i>	<i>22 – 76</i>
<i>UPDRS “on” stimulation score</i>	<i>22(7)</i>	<i>11 – 36</i>
<i>Hours off medication</i>	<i>15(3)</i>	<i>11 – 20</i>

UPDRS – Unified Parkinson's Disease Rating Scale of motor symptom severity

2.7.2 Controls

Healthy controls were recruited from the list of healthy participants lists maintained by the Cognitive Motor Neuroscience Group of the Sobell Department of Motor Neuroscience and Movement Disorders and also through local advertising. They were selected on the basis of good general health, and none had any history of neurological or psychiatric illness, head injury or drug or alcohol misuse. Fifteen potential controls were identified and approached to participate in the study and four refused. Therefore, eleven

healthy controls were included in the study. Demographic characteristics of the two groups are shown in Table 2(b).

Table 2(b). Demographic characteristics of PD patients and controls.

Group	Mean Age (SD)	Mean Education (SD)	Mean IQ (SD)	Mean MMSE (SD)	Handedness Right:Left
PD patients	58 (11)	14 (3)	110 (13)	29 (2)	6:4
Controls	57 (15)	15 (3)	128 (4)	29(1)	10:1

2.7 Procedure

Ethical approval was given for this study by the Joint Ethics Committee of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery. Patient and (Ethical approval can be found in Appendix A). All participants gave informed consent and were assessed in a laboratory using the same procedure by the same investigator (AH). (Patient and Control Consent forms can be found in Appendix B).

To assess the effect of reward on motor performance two different tasks were used; namely the computer-based Simple Reaction Time (SRT) test and the Card Arranging Reward Responsivity Objective Test (CARROT) card sorting test. The DBS patients underwent these tests twice, once with stimulators off and once with stimulators on. The healthy controls also completed the tests twice, so as to control for practice and fatigue effects. All participants also completed a number of additional measures of cognition, mood and personality.

2.7.1 Experimental Tasks

2.7.1.1 Simple Reaction time (SRT)

Equipment

The SRT task entailed the participant making responses on a purpose-made response box, in reaction to a stimulus presented on a computer screen. Responses were made on a box with two buttons, a home key and a response key, illustrated in Figure2(a). The buttons were 2.54 cm in diameter and placed in a vertical row. The buttons were spaced 10.16 cm vertically. This response box was linked to a computer with a 14-inch monitor on which the stimuli were displayed. Demonstration and practice trials were provided before beginning the task.

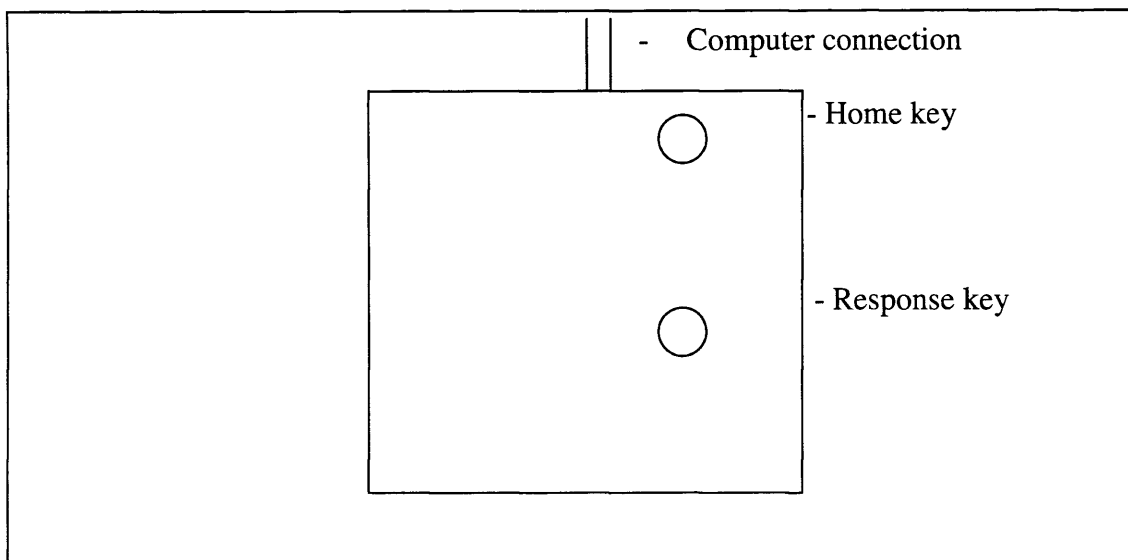


Figure 2(a) The response box with home and response keys.

Warned and unwarned Simple Reaction time

The participants sat in front of the computer monitor and were instructed to hold down the home key with the index finger of their right hand. A fixation cross was presented on the screen and, at intervals; a solid white box (response stimulus) was superimposed on

the fixation cross. The presentation of this stimulus required the participant to respond by lifting their right index finger from the home key and moving to the response key as quickly as possible. They could then move back to the home key in their own time. The screen cleared 500ms after a response was made. The next trial started when the home key was pressed again. Therefore, the participants responded to the presentation of this single stimulus that required the same response across trials, thus allowing pre-programming of the response.

On 50% of trials, before the solid white box (response stimulus) was presented an empty box (warning signal) was superimposed on the fixation cross. This occurred in a randomised manner. After a delay of sixteen hundred milliseconds this box was filled to become solid white, and this constituted the response stimulus. On 50% of trials there was no warning signal and the fixation cross was followed by a solid white box (response stimulus) immediately, in which case the participant was required to press the response key straight away. In all warned trials, the participants were instructed to make use of the warning signal and prepare themselves to respond to presentation of the response stimulus. Participants were also told to wait to respond until presentation of the response stimulus in order to discourage anticipatory responses. Figure 2(b) illustrates the computer screen at the differing stages over the unwarned and warned trials.

Handedness

All patients used their right hand to complete all trials of the SRT task, despite dominant handedness, in order to control for laterality of disease severity (i.e. PD symptoms are

generally more severe on one side than the other). Controls also completed the SRT with their right hand in order to complete the protocol in an identical manner to patients.

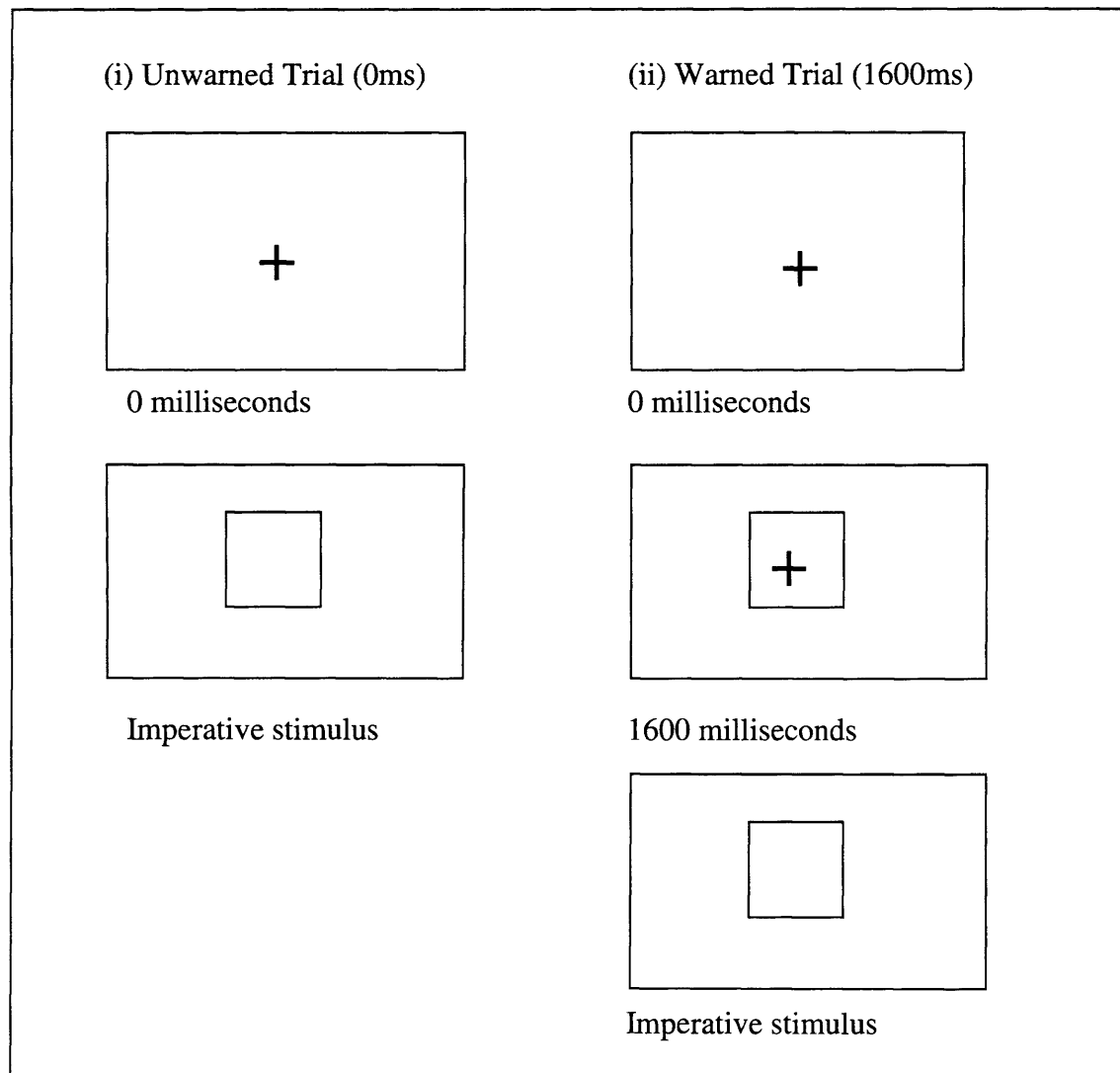


Figure 2(b) The computer screen images for unwarned (i) and warned trials (ii).

Measurement of initiation times and movement times

The time from presentation of the response stimulus to the release of the home key, i.e. the time between presentation of the stimulus and initiation of a response, was measured as the initiation time (IT). The time from release of the home key to pressing the

response key i.e the time between initiating and executing a button press response, was measured as the movement time (MT). Both IT and MT were recorded by the computer to the nearest millisecond.

Reaction time and Reward

Each SRT test entailed four blocks of forty trials of the aforementioned task. Both DBS patients and healthy controls completed two sets of the four block SRT test with breaks in between. Other tasks were completed between the completion of one SRT test and the beginning of the second. The DBS patients completed one SRT test with stimulators on and the other with stimulators off. The order of this was counterbalanced between patients, with the first patient completing his first SRT “off” stimulation and his second “on” stimulation and the next patient completing his first SRT “on” stimulation and his second “off” stimulation etc. Counterbalancing the order of testing sought to address the issue of practice effects amongst the patients. Healthy controls also completed the SRT twice in order to control for potential practice effects.

To assess the impact of reward on motor performance, each task was performed with and without financial incentive. To avoid any biasing the participants were not told in advance that they would receive any reward. The participants completed two blocks of the SRT before they were told that they would receive a reward if they could speed up their reaction times. In blocks one and two participants received no reward for completing the task. In block three they received a 50 pence reward for every 10 milliseconds they speeded up their reaction times. In block four participants received a £1 reward for every 5 milliseconds they speeded up their reaction times. On rewarded

trials, participants were informed of the potential reward for improved performance only before the beginning of that block i.e. participants were not informed of the increased financial reward of block four until they had completed block three. At the end of blocks 2 and 3, participants were provided with feedback and were told what their reaction times for that block had been.

Two incremental rewarded conditions were used in order to ascertain any differences both within the patient group (on stimulation vs off stimulation) and between the patient and control groups and to investigate whether each group, under differing reward conditions, could decrease their minimal reaction time speed, as found by other authors.

2.7.1.2 The CARROT Task

The Card Arranging Reward Responsivity Objective Task (CARROT), (Powell et al, 1996) measures the extent to which patients increase their speed of performance on a simple psycho-motor task when offered a small financial incentive. Therefore, the test is designed to index incentive reward responsiveness (Richardson, Powell & Curran, 2003). Participants were given a stack of cards, each with five single digits printed on them, one number in each corner and one number in the centre. The numbers on the cards were between one and nine, inclusive, and the cards have combination of all of those numbers. However, on each card a number 1 or a number 2 or a number 3 appeared, and no combination of these numbers appeared on any one card. The aim of the task is to sort the cards as quickly as possible into stacks of 1, 2 and 3 contingent on whether one of the numbers on the card is 1, 2 or 3. The participants had four trials of sorting the cards as quickly as possible into stacks of 1, 2 and 3. On the first trial the

participants sorted 60 cards to measure baseline speed. On trials two, three and four the participants were given one hundred cards. Trials two and four measured unrewarded speed and trial three measures rewarded speed, i.e. speed of performance with expectation of financial incentive; namely 10p for every five cards correctly sorted. To avoid any biasing the participants were not told in advance that they would receive any reward. The participants completed two blocks of card sorting before they were told that they would receive a reward if they could speed up their performance.

2.7.2 Clinical Measures

The assessment of the patient and control groups was identical, with the exception of the Unified Parkinson's Disease Rating Scale (UPRDS), an assessment of the severity of the motor symptoms in Parkinson's disease, which was only completed for the patient group. To assess individual differences as well as possible between groups differences in mood, cognitive status and sensitivity to reward, the following additional measures were used.

Handedness

The Edinburgh Handedness Inventory (Oldfield et al, 1971) was used to assess the extent of right-handedness of each participant.

Beck depression inventory (BDI)

As depression may affect reaction times, the Beck Depression Inventory (BDI) was used to screen for the presence and extent of clinical depression for each participant. The BDI, (Beck, 1974) is a 21-item scale, which assess the affective, cognitive, behavioural

and somatic aspects of depression. The scores range from 0 to 63, with higher scores indicating more severe self-reported depression. Scores above 18 are considered to indicate moderate to severe depression.

Marin Apathy Scale

As apathy may affect reaction times the presence and extent of apathy was assessed for each participant. The Marin Apathy Scale (Marin, 1990) is an 18-item scale that probes different aspects of apathy on a 0 – 3 scale. Some items are reversed scored. Scores range from 0 to 54 with higher scores indicating greater apathy. Scores above 14 are considered to reflect clinical levels of apathy.

Mini Mental State Examination (MMSE)

The Mini Mental State Examination (MMSE) (Folstein, Robinson, Folstein & McHugh, 1985) is a brief screening instrument for cognitive impairment consisting of twenty items. The test is comprised of questions related to working memory, language, praxis orientation and attention (Lezak, 2004). Scores range from 0 to 30, with lower scores indicative of greater cognitive impairment. Scores below 25 are considered to reflect cognitive impairment.

Wechsler Abbreviated Scale of Intelligence (WASI)

The vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence WASI (Wechsler, 1999) were used to obtain a measure of intelligence.

Tridimensional Personality Questionnaire

The Tridimensional Personality Questionnaire (Cloninger et al, 1991) is a validated 100 item questionnaire which assesses three dimensions of personality: responsiveness to reward, harm avoidance and novelty seeking, according to patient responses to specific statements. Responses to each statement are in a “yes”/ “no” format. The TPQ was used here in order to obtain an additional measure of responsiveness to reward, for the patient and control groups separately.

Unified Parkinson's disease Rating Scale (UPDRS)

The UPDRS is a clinical rating scale used to measure the severity of the motor symptoms of Parkinson's disease. The UPDRS was completed on each patient at the time of their assessment while off medication and with DBS on and off. The scale includes the assessment of fourteen aspects of motor functions, including gait, balance, and the assessment of strength and dexterity of the hands, arms, legs and feet, each scored on a four-point scale, with a minimum score of zero maximum score of fifty-six. AH, was trained on this assessment by a neurologist (IMT). If patients had completed this assessment in clinic with neurologist IMT within three months of entering the study it was not repeated and clinic scores were used, as scores on this scale do not vary considerably within this time period.

2.8 Statistical analysis

Mixed model ANOVA's were used to compare reaction times across unrewarded and rewarded conditions to determine the effect of DBS and reward. Group (PD patients and healthy controls) was used as the between groups variable and Stimulation (DBS on vs

off or task repetition), Reward (presence vs absence) were used as the within subject repeated measures variables for analysis of the IT and MT data. Post-hoc Pairwise comparisons with Bonferroni correction were performed to further analyse the data shown as significant by the ANOVA. Paired samples t-tests were used to further compare the mean response times within groups over rewarded vs unrewarded conditions for significant interactions.

Paired samples t-tests were used to compare the mean scores on the CARROT card-sorting task to assess any differences in reward responsiveness across stimulation for patients and repetition for controls. Pearson correlations were used to determine the presence of any significant relationships between reward responsiveness, as measured by performance on the SRT and CARROT tasks and clinical measures relevant to motivation and reward.

RESULTS

The PD patients and healthy control groups did not differ significantly in terms of age, education, cognitive status or depression.

None of the patients or controls reached clinical caseness for depression (scores above 18), as determined by responses to the Beck Depression Inventory (BDI). None of the patients or controls were cognitively impaired as determined by performance on the Mini Mental State Examination (MMSE) (scores below 25). The two groups differed significantly in terms of apathy ($p = 0.019$), with patients having a higher average apathy score than controls, and eight of the ten patients reached clinical caseness criteria (scores

above 14) for apathy. However apathy was not a significant covariate between the groups ($p = 0.475$). The analysis was completed separately for Initiation times and Movement times.

The data was not normally distributed; however transformation was not possible as there were skews in both directions on different repeats of the same data. Therefore, parametric mixed model ANOVA's were used to analyse the data, as there is no equivalent non-parametric test, and the ANOVA is robust to this problem. The conservative Bonferroni Correction was also used to ensure reliability of pairwise comparisons.

2.9 Initiation time

2.9.1 Effect of Warning Signal on Initiation Time (IT)

To assess the effect of a warning signal on IT a mixed model ANOVA was completed with Group (PD vs controls) as the between subjects variable and DBS (on vs off for patients or time 1 vs 2 for controls) x Warning Signal (0 ms SRT vs 1600 ms SRT) x Reward (mean of rewarded blocks vs mean of unrewarded blocks) as the within subjects variables. The results of this analysis showed that, as expected, the main effect of warning signal was significant ($F(1, 19) = 103.140$; $p = 0.001$), such that IT with warned trials were significantly faster than unwarned trials across all groups and conditions; however none of the interactions between warning signal and the other variables were significant ($p > 0.05$). Therefore, in subsequent analyses data were collapsed across the two warning intervals.

2.9.2 Effect of Group, Deep Brain Stimulation (DBS)/ Repetition and Reward, on Initiation Time (IT)

To assess the effects of Group, Stimulation/ Repetition and Reward on IT a mixed model ANOVA was completed with Group (PD vs controls) as the between subjects variable and DBS/Repetition (on vs off for patients or time 1 vs 2 for controls), Reward (mean of two rewarded blocks vs mean of two unrewarded blocks) as the within subject variables. The main effect of Group was significant ($F(1, 19) = 31.19$ $p = 0.001$), as the patients had slower IT across all conditions than the controls. The Stimulation/Repetition main effect was significant ($F(1, 19) = 4.96$ $p = 0.038$). The main effect of Reward was significant ($F(1, 19) = 21.46$, $p = 0.001$), indicating that across the two groups IT for the rewarded blocks were significantly faster than IT for the unrewarded blocks. The Group x DBS/Repetition interaction shown in Figure 2(c) approached significance ($F(1, 19) = 3.277$ $p = 0.086$). The DBS/Repetition x Reward ($p = 0.426$) interaction, and the Group x Reward interaction ($p = 0.121$) were not significant. The Group x DBS/Repetition x Reward interaction was also not significant ($p = 0.263$).

To break down the significant main effects of stimulation and reward a number of post-hoc analyses were completed. Stimulation (DBS on vs off) had a significant effect on IT for the patients ($p = 0.012$). Repeated performance (time 1 vs 2) did not have a significant effect on IT for the controls ($p = 0.766$). Reward had a significant effect on IT for both patients ($p = 0.001$) and controls ($p = 0.042$).

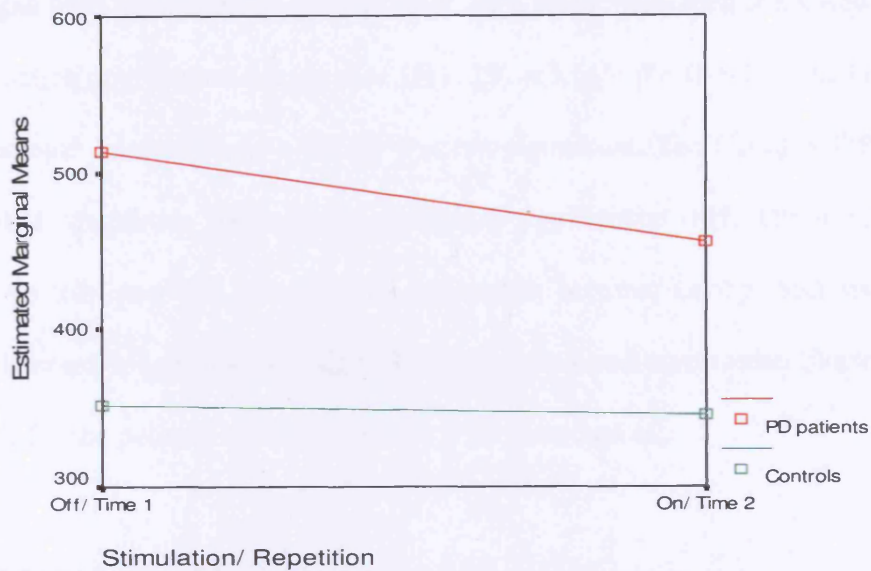


Figure 2(c) Illustrating the Groupx DBS/ Repetition interaction, which approached significance. Stimulation (DBS On/ Off) on Initiation time in the patient group and Repetition (Time 1 vs Time 2) in the Control Group.

2.9.3 Effect of Reward Magnitude on IT

To examine the effect of reward magnitude (50 p vs £1) on IT, IT for Block 3 (50 p reward per 10 ms IT speeding) and block 4 (£1 reward per 5 ms IT speeding) were compared across the two Groups (PD vs Controls) and for the two DBS/Repetition conditions (on vs off for patients, time 1 vs 2 for controls). A mixed model ANOVA was completed with Group (PD vs controls) as the between subjects variable and DBS/Repetition (on vs off or time 1 vs 2), and Reward Magnitude (50p vs £1) as the within subjects variables.

The main and interaction effects of Reward Magnitude were as follows. The main effect of reward magnitude was not significant ($p = 0.515$), indicating that across the two groups the IT for the high level reward block (£1) was not significantly faster than IT for

the low level reward block (50p) (Figure 2(g). The DBS/Repetition x Reward Magnitude interaction approached significance ($F(1, 19) = 3.645$; $p = 0.071$). The Group x Reward Magnitude interaction ($p = 0.234$) was not significant. The Group x DBS/Repetition x Reward Magnitude interaction approached significance ($F(1, 19) = 3.527$; $p=0.076$). Figures 2(h) and 2(i) illustrate the interaction between Group, Stimulation/Repetition and Reward Magnitude, showing IT for rewarded and unrewarded blocks with DBS on vs off for the patients and for time 1 vs 2 for the controls.

2.9.4 Correlation of Initiation time and Clinical Measures

Pearson correlations were used to determine if unrewarded and rewarded initiation times and scores on the CARROT card-sorting test, indicating reward responsiveness correlated with the clinical measures relevant to motivation and reward responsiveness within the patient and controls groups. The analysis was conducted upon the groups separately. These measures were presence/absence of apathy, as determined by the scores on the Marin Apathy Scale. Correlation between reward dependence and unrewarded and rewarded initiation times and scores on the CARROT card-sorting test was determined by scores on the Tridimensional personality questionnaire (TPQ). The TPQ is a 100-item questionnaire that identifies personality traits including reward dependence. As multiple correlations were carried out the Bonferroni correction was used. No significant correlations were found, indicating that no significant relationships existed between initiation times, reward responsiveness and the presence/ absence of apathy.

2.10 Movement Time

2.10.1 Effect of Warning Signal on Movement Time (MT)

To assess the effect of a warning signal on MT a mixed model ANOVA was completed with Group (PD vs controls) as the between subjects variable and DBS (on vs off for patients or time 1 vs 2 for controls) x Warning Signal (0 ms SRT vs 1600 ms SRT) x Reward (mean of rewarded blocks vs mean of unrewarded blocks) as the within subjects variables. The results of this analysis showed that the main effect of warning signal was not significant ($p = 0.085$), such that MT with warned trials were not significantly faster than unwarned trials across all groups and conditions; however none of the interactions between warning signal and the other variables were significant ($p > 0.05$). Therefore, in subsequent analyses data were collapsed across the two warning intervals.

2.10.2 Effect of Deep Brain Stimulation/ Repetition, Reward and Group on Movement Time (MT)

To assess the effects of Group, Stimulation/ Repetition and Reward on MT a mixed model ANOVA was completed with Group (DBS patients and controls) as the between subjects variable and Stimulation/Repetition (on vs off or time 1 vs 2) and Reward (mean of unrewarded blocks vs mean of rewarded blocks) as the within subjects variables. MT was estimated as the time it took between the participant lifting his/her finger from the response key and pressing the target key upon presentation of the imperative stimulus.

The main effect of Group was significant ($F(1, 19) = 38.019$; $p = 0.001$), as the patients had slower MT across all conditions than the controls. The main effect of

Stimulation/Repetition was significant ($F(1, 19) = 38.66$; $p = 0.001$). The main effect of Reward was not significant ($F(1,19) = 1.68$; $p=0.210$), indicating that across the two groups MT for the rewarded blocks was not significantly faster than MT for the unrewarded blocks. The Group x DBS/Repetition interaction, shown in figure 2(d) was significant ($F(1, 19) = 38.78$; $p = 0.001$), as patients had slower MT across all conditions than controls. The DBS/Repetition x Reward ($F(1, 19) = 5.37$; $p = 0.032$) interaction was significant. However, the Group x Reward ($p=0.614$) was not significant. The Group x DBS/Repetition x Reward interaction was significant ($F(1,19)=7.41$, $p=0.015$).

To break down the significant Group x DBS/Repetition x Reward interaction, a number of post-hoc analyses were completed. Stimulation (DBS on vs off) had a significant effect on MT for the patients ($p = 0.001$). Repeated performance did not have a significant effect on MT for the controls ($p = 0.992$). Reward did not have a significant effect on MT for the patients ($p = 0.227$) or controls ($p = 0.576$). For the patients, paired samples T-tests were completed to ascertain any differences in MT between DBS on vs off for the unrewarded and rewarded blocks separately. Patients' MT was significantly faster with DBS on vs off for both the unrewarded block ($t(9) = -6.435$; $p = 0.000$) and for the rewarded block ($t(9) = -5.857$; $p = 0.001$). Similarly, for the controls, paired samples T-tests were completed to ascertain any differences in MT between Repetition (time 1 vs 2) for the unrewarded and rewarded blocks separately. No significant effect of Repetition was found for the controls on either the unrewarded ($p = 0.866$) or rewarded ($p = 0.870$) blocks.

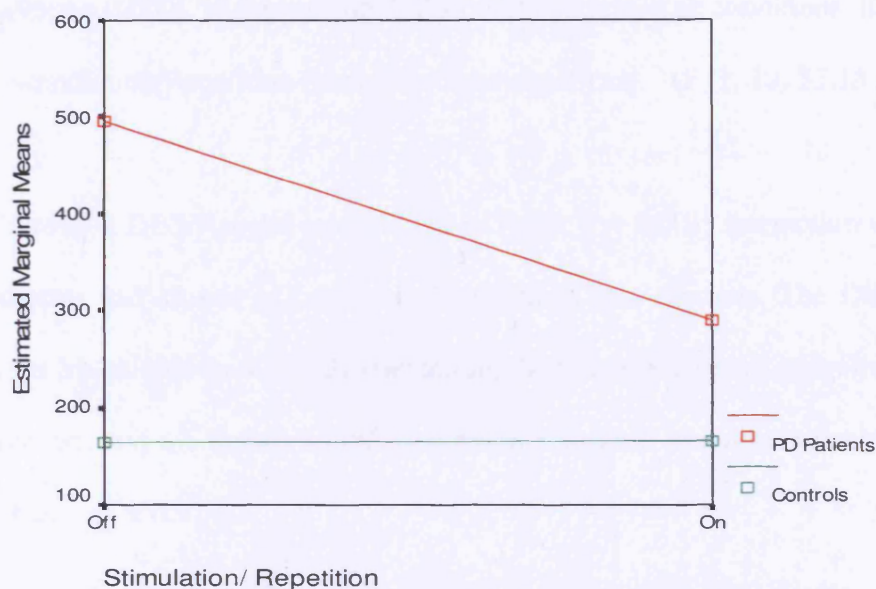


Figure 2(d). Illustrates the significant Group x DBS/Repetition interaction. Stimulation/ Repetition on Movement times in patient and control group.

2.10.3 Effect of Reward Magnitude on MT

To examine the effect of magnitude of reward (50 p vs £1) on MTs, MT for Block 3 (50p reward per 10 ms IT speeding) and block 4 (£1 reward per 5 ms MT speeding) were compared across the two Groups (PD vs Controls) and for the two DBS/Repetition conditions (On vs off, time 1 vs 2). A mixed model ANOVA with Group (PD vs controls) as the between groups variable and DBS/Repetition (on vs off or time 1 vs 2), Reward magnitude (50p vs £1) as the within subject repeated measures variables.

The main and interaction effects of Reward Magnitude were as follows. The main effect of reward magnitude was not significant ($p = 0.716$), indicating that across the two groups the MT for the high level reward block (£1) was not significantly faster than MT for the low level reward block (50p). The main effect of Group was significant ($F(1, 19)$

= 40.95; $p = 0.000$), as the patients had slower MT across all conditions than the controls.

The Stimulation/Repetition main effect was significant ($F(1, 19) = 33.15$, $p = 0.001$).

The Group x DBS/Repetition ($F(1, 19) = 34.01$; $p = 0.001$) interaction was significant, as patients had slower MT across all conditions than controls. The DBS/Repetition x Reward Magnitude ($p = 0.632$) interaction, the Group x Reward Magnitude ($p = 0.227$) interaction, and the Group x DBS/Repetition x Reward Magnitude interaction were not significant ($p = 0.974$).

2.10.4 Correlation of Movement time and Clinical Measures

Pearson correlations were used to determine if unrewarded and rewarded movement times and scores on the CARROT card-sorting test, indicating reward responsiveness correlated with the clinical measures relevant to motivation and reward responsiveness within the patient and controls groups. The analysis was conducted upon the groups separately. These measures were presence/absence of apathy, as determined by the scores on the Marin Apathy Scale. Correlation between reward dependence and unrewarded and rewarded movement times and scores on the CARROT card-sorting test was determined by scores on the Tridimensional personality questionnaire (TPQ). The TPQ is a 100-item questionnaire that identifies personality traits including reward dependence. As multiple correlations were carried out the Bonferroni correction was used. No significant correlations were found, indicating that no significant relationships existed between movement times, reward responsiveness and the presence/ absence of apathy.

2.11 The CARROT task

No significant differences were found between patient performances “on” and “off” stimulation ($p=0.239$) on the CARROT (Card arranging reward responsivity objective test), indicating that patients performance on this task was not significantly faster in the “on” stimulation condition compared with the “off” stimulation condition. No significant differences were found between control performances at “time 1” and “time 2” ($p=0.937$), indicating that there were no significant effects of practice on controls’ performance on this task.

Discussion

The main findings of this study were:

- *Patients initiation time showed a trend towards improvement and movement time (MT) was significantly faster on stimulation compared to off stimulation.*
- *The presence of reward resulted in a significant speeding up of IT*
- Stimulation did not significantly effect patients initiation time in response to reward conditions to a greater extent than repetition effected controls initiation time in response to reward
- Stimulation did not effect patients performance on the CARROT card-sorting task in response to reward conditions to a greater extent than repetition effected controls performance on this task in response to reward.
- *The presence of a warning signal significantly improved patients initiation time.*

Overall, patients IT and MT were slower than controls in all conditions, which is in accordance with the findings of other authors (de Frias, Dixon, Fisher & Camicioli, 2007; Jahanshahi et al; 2001; Kutukcu et al, 1999; Mazzucchi et al, 1993).

2.12 The Effect of Stimulation on Reaction Time

Hypothesis 1 STN DBS would speed up IT and MT for patients in the “on” stimulation condition as compared with the “off” stimulation condition.

The results suggest a trend towards improvement in patients IT, and a significant improvement in patients MT in the “on” stimulation condition as compared with the “off” stimulation condition. These findings are in accordance with the findings of other authors, who found improvement in response times under stimulation (Ellrichman et al, 2008; Kumru et al, 2004; Temel et al, 2006). It should be noted that although only a trend towards statistical significance was found for improvement in IT, these results are reported in the context of a small sample size. No significant practice effects were seen for controls on IT or MT. This finding, and the counter-balanced design of the study, which was used to minimise the effects of practice, suggests that improvements seen in the patient sample were due to the effects of stimulation, as opposed to repeated performance of the IT tasks or practice.

However, although counter-balancing of patients was used to reduce practice effects, the analysis was conducted on the patients off stimulation and on stimulation assessments compared with the controls time 1 and time 2 respectively, thereby comparing both groups “worst” and “best” performances. Therefore, although the results suggest a trend towards improvement in patient response times as compared with the control group, this is complicated by the potential practice effects within the patient group. However, although this complicates the comparison of results between the patient and control groups, it was necessary to counter-balance in this manner, so as to decipher the effects of stimulation as opposed to the effects of practice had they not been counter-balanced.

The results obtained, therefore, suggest that stimulation results in some improvement in initiation time, namely the premovement process. However, it appears that stimulation results in significant improvement in movement time, namely the motor process.

2.13 The Effect of Reward on Reaction Time

Hypothesis 2. The presence of reward would speed up IT in patients and controls

This hypothesis was supported as IT was improved in response to reward availability. This finding supports the findings of other authors (Evarts et al, 1981; Mir et al, In press). The main effect of reward on IT was significant across both groups, indicating a general significant speeding of initiation times in response to reward. Further analysis revealed significant speeding of initiation times in response to reward for each group individually.

The results, therefore, show that the participants (both healthy controls and PD patients) could improve their initiation times in the presence of reward. This finding is in accordance with the concept of paradoxical kinesia and reflects the findings of Ballenger et al (2006) and Niv et al (2007), who found that healthy controls and PD patients respectively, could exceed their maximal self-determined speed of response in the context of external cues and urgent situations. Ballenger et al (2006) suggested that although paradoxical kinesia has been identified in PD, this phenomenon is not necessarily just a feature of disease but may be a general hallmark of the motor system, and these results support this.

Paradoxical kinesis often occurs in response to urgent or dangerous stimuli, however, as the participants were not responding to dangerous stimuli but to monetary incentive, it may be concluded that the financial reward presented was a sufficient motivator to enable patients to speed their reaction times. This implicates the involvement of the Anterior Cingulate Circuit (ACC) which mediates motivation through neural pathways between the basal ganglia and the frontal cortex (Bonelli & Cummings, 2007).

Studies highlight the role of the basal ganglia in reward related behaviours and implicate dopamine in reward anticipation and reward-related information processing and decision making (Arias-Carrion & Poppel, 2007; Berridge & Robinson, 2003; Nieoullon & Coquerel, 2003; Tricomi et al, 2004). It has been suggested that dopamine deficiency may cause aberrant decision-making (Niv et al, 2007). Contrary to the findings of other authors (de Frias et al, 2007; Kutukcu et al, 1999; Mazzucchi et al, 1993) who found that reaction times in PD are impaired relative to healthy controls, Mazzoni, Hristova, and Walker (2007) found that PD patients were generally as accurate and fast as controls on simple movement tasks. The authors concluded that dopamine deficiency in PD may cause aberrant implicit decision-making, resulting in increased sensitivity to the energetic demands of movement; namely that PD patients implicitly overestimate the energy required to perform a movement, which results in them generally performing below their level of ability (Mazzoni et al, 2007).

The current findings suggest that in the presence of a sufficiently motivating reward in the form of monetary incentive, movement initiation can be speeded up in PD, possibly through shifting the cost vs benefit balance in relation to the energetic demands of fast

movement. This improvement of speed of reaction is in accordance with the findings of Mazzoni et al (2007).

The current findings also suggest that there is a differentiation between the pre-movement process and the execution of the movement in response to reward, as initiation times were affected by reward availability and movement times were not. Therefore the level of improvement appears to have occurred at the motor planning level, indicating the involvement of cognitive and motivational factors. This finding is in accordance with those of Mir et al (In press), who found greater improvement in IT of healthy controls than MT.

Brown and Pluck (2000) postulated a neuro-cognitive formulation of goal-directed behaviour; that is purposeful behaviour which is driven towards the attainment of a specific goal. Figure 3(a) illustrates this model. The current findings, therefore, may be understood in the context of this model, where motivational processes and properties influence the initiation of action across the groups. In the presence of a potential reward participants may select and prepare the relevant motor programmes prior to the presentation of the go stimulus in a more consistent fashion across trials. In PD patients this may, therefore, avoid the implicit energetic cost biases hypothesised by Mazzoni et al (2007). The SRT tasks entail the repeated response of one movement to one stimulus, thus allowing for the pre-programming of movement, which further supports this hypothesis.

Figure 3(a). Pluck and Brown's (2000) model of the processes involved in goal directed behaviour.

However, although presence of reward significantly improved IT, reward magnitude had no significant effect on IT, as patients and controls did not improve their IT in response to the second, higher level of reward. It may be the case, therefore, that have increased their IT at the first reward level, they reached their maximal or "ceiling" level of performance.

2.14 The Effect of Stimulation on Reward Responsiveness

Hypothesis 3. STN DBS would have a differential effect on reward responsiveness of patients IT over and above any change of IT with repeated performance in the control group

This hypothesis was not supported, as stimulation did not have a significant effect on patients responsiveness to reward in terms of improved IT. No practice effects on IT were seen for the controls. Therefore STN DBS did not have a differential effect on patients reward responsiveness in relation to control performance.

Hypothesis 4. STN DBS would have a differential effect on reward responsiveness of patients over and above any change of reward responsiveness with repeated performance in the control group, as assessed by performance on the CARROT card-sorting task.

This hypothesis was not supported, as stimulation did not have a significant effect on patients' responsiveness to reward in terms of improved performance on the CARROT card-sorting task. No practice effects on repeated performance of this task were seen for the controls. Therefore STN DBS did not have a differential effect on patients reward responsiveness in relation to control performance.

These results suggests that, although STN DBS has effects on the motor frontal-subcortical circuit, stimulation does not influence the motivational frontal-subcortical circuit, the ACC, as no significant effects in reward responsiveness were found "on" stimulation. This suggests that STN DBS had no modulating effect on motivation in PD patients. This is contrary to the findings of other authors, some of whom found that STN DBS had detrimental effects on motivation, in the context of emergence or worsening of pre-existing apathy, which, in PD, is characterised by an isolated lack of motivation (Drapier et al, 2005; Funkiewiez et al, 2004; Saint-Cyr et al, 2000; Schupbach et al,

2005; Temel et al, 2006). Other authors, however, have reported improvement in motivation after STN DBS (Contarino et al, 2006; Czernecki et al, 2005).

The current findings support the results of Castelli et al (2006), who found that apathy was stable after STN DBS, at 15 month follow-up, indicating that stimulation had no effect on motivation. The findings here may reflect that DBS has no genuine acute effects on motivation, however certain methodological issues may also account for this result, including small sample size and how representative the patient sample may be of the wider DBS-treated PD population. These issues will be discussed further below with reference to methodological issues.

The absence of any effect of stimulation on reward responsiveness can potentially inform us about the mechanism of action of DBS on the STN. It has been suggested that DBS of the STN acts a functional lesion in this area, thereby limiting the output of the STN. In a study of the effects of focal basal ganglia lesions on reward responsiveness Schmidt et al (2008) found that patients with basal ganglia lesions fail to differentiate between monetary incentives, and are therefore were less responsive to reward. If STN DBS operated as a functional lesion, it would be expected that reward responsiveness of PD patients with STN DBS to be impaired, as compared to controls, however this was not the case, as the results show that patients' reward responsiveness was not impaired "on" stimulation. Therefore, the current findings suggest that DBS of the STN may operate in a manner other than as a functional lesion.

2.15 The effect of warning signal on Reaction time

Hypothesis 5. The presence of a warning signal would improve patients initiation time.

Overall, patients initiation times benefited from a warning signal, which reflects the findings of other studies e.g. Jahanshahi et al, (1992). From the results obtained here, it is apparent that both patients and controls benefited from the presence of warning signal in terms of initiation time, however, the presence of a warning signal had no significant effect on movement time. This does not support the hypothesis that of Jahanshahi et al (1992), who suggested that patients with PD are selectively more reliant on a warning signal to maintain motor readiness. Therefore, it may be concluded that, generally, the presence of a warning signal allows participants, both PD and healthy controls, to prepare and maintain motor readiness.

2.16 Dopamine and Reaction Time

The patients in this study completed all tests off their dopaminergic medication and had been off their dopamine medication for an average of fifteen hours; yet they managed to improve their responses in the presence of reward. This is contrary to the findings of Czernecki et al (2002), who found that PD patients in the “off” medication state had lower motivation in response to reward. However this finding supports those of Jahanshahi et al (1993), who found that reaction times in PD were not dopamine dependent, suggesting that slowness of IT may represent brain dysfunction rather than dopamine deficiency. The findings of this study implicate the involvement of non-dopaminergic circuits in reward related behaviours, as suggested by Lalonde & Botez-Marquard (1997).

2.17 Apathy

As expected, the PD patients' scores on the Marin Apathy Scale (Marin, 1990) were higher than controls. This supports the findings of other authors (e.g. Czernecki, 2002) and suggests that, even in the absence of depression or dementia, apathy is evident in PD, and can persist or newly present after STN DBS surgery. Although some authors have found stability of apathy (Castelli et al, 2006) and improvement of apathy after surgery (Czernecki et al, 2005), a number of authors have found apathy to newly present (Funkewiez et al, 2004; Saint-Cyr et al, 2000; Schupbach et al, 2005) or worsen (Drapier et al, 2005; Funkewiez et al, 2004) after STN DBS.

The high levels of apathy in this study may also be understood in the context of a chronic a-priori effect of DBS on the ACC and motivation. The ACC mediates motivation and is often impaired in PD, resulting in apathy syndromes (Pluck and Brown, 2000) and the influence of STN DBS on these circuits has been suggested by other authors (Czernecki et al, 2005). However, speculation about the origins of apathy in this patient sample is tentative, as the pre-operative apathy levels in the patient sample are unknown. The high levels of apathy found here may equally reflect pre-operative apathy, resulting from the PD disease process and related dopamine deficiency, as suggested by other authors, (Czernecki et al, 2002) as opposed to apathy arising from DBS.

2.18 Study limitations

There are a number of limitations to this study, due to restrictions of both time and patient population. One such limitation was the small sample size of the study.

Recruitment difficulties were anticipated, as the patient population is small and the nature of the study necessitated an extensive period of time both off stimulation and off medication for the patients, which excluded a large number of potential patients who would not be able to tolerate their symptoms in this context. This also leads to the issue of generalisability of the results, which is another potential limitation to this study, as the patients included in the study had little tremor off stimulation and medication and so may not fully reflect the general population of DBS patients who present with more disabling motor symptoms. The issue of generalisability of the results also highlights the limitation of the levels of apathy found in the DBS sample. The majority of the patient sample in this study reached clinical caseness for apathy. This may reflect the influence of STN DBS on apathy; however the patients in this study may represent a sub-group of high-apathy PD patients. These limitations could be rectified with larger samples in future research.

The ethical issues arising around switching off of patients stimulators are another limitation of this study. In order to cause as little discomfort as possible to patients and to comply with the ethical considerations of the study patients were switched off stimulation for an average of approximately 45 minutes. Patients were relied on to determine when they were fully “off” stimulation, usually waiting approximately ten minutes until commencing testing. Other studies however, had longer duration “off” periods to ensure patients were off stimulation and that performance was not the result of any residual effects of stimulation. This was not possible here, however the current findings may have been more robust had this approach been implemented.

It appears intuitive that money is an incentive and would therefore act as a reward, and in this study money appears to have been a motivating influence to speed response times. However, money may not have the same reward value to all individuals. The participants did not increase their IT at the second, higher reward level, which may have been the result of a “ceiling” effect; however it may be the case that the initial improvement in IT was not the result of reward-related behaviour but influenced by other factors. Therefore, a potential change I would make to this study would be the inclusion of different types of reward to assess any potential differential effects that may occur.

Patient handedness is another limitation of the study, as due to time limitations and patient eligibility to participate; left-handed patients were also included in the study. The ratio of right handed to left handed patients was 60:40. The necessity of using both right and left handed patients in the study may have had an impact on the results obtained, as all patients completed tests with their right hand. Differences in dominant handedness may complicate the interpretation of results, as participants who used their non-dominant hands may have had slower reaction times on that basis. However, it was necessary for patients to only use their right hand as this controlled for any effects of disease laterality (i.e. PD symptoms are generally worse on one side than the other).

Practice effects are another issue which may also complicate the interpretation of the results obtained here. In order to control for any practice effects within the patient group a counter-balanced design was used, with one patient commencing testing “off” stimulation and the next commencing “on” stimulation. The results of patients “off” and

“on” stimulation were analysed with the results of controls time 1 and time 2 respectively. The results were analysed in this manner so as to assess the performance of both groups at their “worst” (off stimulation for patients/ time 1 for controls) and best (on stimulation for patients/ time 2 for controls). Therefore the results of half of these patients were from their second set of testing. Although this somewhat complicates the results, it was necessary to counterbalance the design in order to control for practice effects within group and it was considered that despite half of the patients potentially gaining from practice effects within group, this would not sufficiently influence their performance due to their level of disability off stimulation.

2.19 Summary and Conclusions

As anticipated, the results show that STN DBS improves IT and MT in PD patients. This finding and the improvements in motor symptoms, as examined by UPDRS assessment, indicate that STN DBS is an effective treatment for the motor symptoms found in advanced PD.

Participants improved their IT in the presence of reward, indicating that PD patients can increase their maximal speed of response in the presence of reward in the absence of dopaminergic medication. This points to the role of non-dopaminergic networks, for example the cholinergic system, in motivation/ reward responsiveness, as suggested by other authors.

STN DBS has overt effects on the motor frontal-subcortical circuit, with obvious results manifested in improvement in motor function. However, the potential effect of STN

DBS on cognitive, affective and motivational circuits remains controversial. In this study, no significant effects of STN DBS on reward responsiveness were found, suggesting a lack of effect on upon the motivational ACC, as no behavioural changes attributable to DBS were seen in response to reward. However, the sample in this study was small and the majority of patients reported clinical levels of apathy, which may indicate that their performance represents a subgroup of apathetic PD patients, and so may not reflect reward responsiveness in the wider PD population who have undergone DBS.

Alternatively, the high levels of apathy seen in this group may result from chronic STN DBS or pre-operative apathy, as found by other authors. It was not possible to assess this here, as pre-operative apathy assessment was not carried out. The results indicate that future studies should consider a longitudinal approach to differentiate the potential acute effects of STN DBS on reward responsiveness and underlying motivational circuits and the longer-term effects of chronic STN DBS on apathy.

Future studies should, therefore, firstly ascertain the effects of STN DBS on the patient group through comparison of pre and post-operative apathy assessment and secondly to investigate the acute effects of STN DBS on reward responsiveness on the sub-groups of apathetic vs non-apathetic patients. Such an approach would also enable the differentiation of the effects of STN DBS on the differing frontal-subcortical circuits, in order to better understand the exact mechanism by which DBS may affect reward responsiveness, motivation, and apathy. The inclusion of an additional control group of medically treated patients with PD who have not undergone DBS surgery would have

been a valuable addition to the study; however, it was not possible in this instance due to time limitations. This is an area of potential further development of the current research that could further inform us about the nature of reward responsiveness and apathy in PD across different treatment modalities and the mechanism of STN DBS on the frontal subcortical circuits.

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Part 3. Critical Appraisal

In this section the background of this study will be further discussed. The strengths and weaknesses of the study will also be discussed along with potential impact of weakness on the results and potential changes that could be made to overcome such limitations.

3.1 Background to this study

The current study developed from research focussing on reaction time deficits in Dystonia and reward responsivity of healthy controls. The thinking behind it arose from the impact of stimulation on the motivational circuits and neurotransmitters that mediate reward responsiveness in healthy people, which are often found to be impaired in Parkinson's disease (PD). I was initially interested in this area because of its focus on the neuropsychological outcomes of a recently developed neurosurgical technique, namely DBS, and how these outcomes could further inform us about the functioning of underlying neural circuits. I have a long standing interest in the neuropsychological and neuropsychiatric side effects of surgery and the prospect of assessing the behavioural manifestations of, not only surgery, but electrical manipulation of specific brain areas presented a unique opportunity.

3.1.1 My experience of conducting this research

Conducting this study has been a rewarding and challenging experience. One of the many rewarding features of this research for me was that it allowed me to meet with patients who had undergone DBS surgery. I found that the patients involved were incredibly giving and selfless with their time and efforts despite undergoing difficult experiences, namely having their stimulators switched off, during the research.

As Deep Brain Stimulation (DBS) is still in relative infancy and undergoing further development, the choices made regarding inclusion and exclusion criteria for the patients involved were not only based upon scientific principals but also had to take into account the ethical considerations that working with this group brought up. These ethical considerations continued to arise during the data collection period, as although the patients who were approached to participate consented freely to take part in the study often their participation brought up difficult realities for both the patients and for myself, namely witnessing the progression of their disease. This was one of the more personally challenging elements of conducting this study.

As aforementioned, the generosity of the patients involved was immense, as they contributed a significant amount of time and effort to participate. However, some of the patients involved had not had their stimulators switched off in some time, e.g.: six months to a year and some had not experienced this at all. On these occasions, the patients often commented on the how the disease had progressed. Although they were aware that the surgery did not halt the progression of their PD, it seemed that, upon switching off the stimulators, there was a realisation for some patients, that the disease was advancing further and that the surgery was only providing symptomatic relief of their an often aggressive disease. I found this difficult to witness, especially as this realisation seemed to occur in the context of the research. On the occasions when this happened, and when the patients wanted to discuss this, I listened to their concerns and feelings of uncertainty about their disease.

This ethical issue was an unexpected element of the research process and one which I would take into consideration regarding future research. Although it was possible for me to discuss the patient's concerns regarding the advancement of their disease, it seemed that when the realisation of their current stage of their PD occurred patients were quite taken aback. This left me with a feeling of responsibility, in terms of patient selection and after-care, which has subsequently effected how I would consider conducting the research in the future. It highlighted to me the necessity of understanding the patient's psychological background prior to entry into the study and any difficulties they may have experienced with regard to adjustment to their physical health condition, as witnessing any advancement in their illness could impact on adjustment and any psychological disorder that may already be present.

Therefore, although the patients were selected in close collaboration with their consultants and nurses, I would consider this issue even further with these teams in the future. It would be important also, that not only patients with pre-existing psychological difficulties or health related adjustment or anxiety issues be considered, as conducting this study highlighted to me the importance of availability of psychological after-care for all patients, if required. I was not in a position to provide this in this situation; however, in terms of further research I consider this to be an important ethical matter.

Teamed with this experience, however, I also witnessed why the DBS patients were so generous with their time and willing to undergo discomfort for the sake of scientific study. This occurred successively from when I met with the first DBS patient;

witnessing him walk independently into the room and, upon switching off stimulation, witnessing him suffer disabling paralysis, spasm and tremor; the impact was overawing.

The experience of conducting this research has highlighted to me the importance of these procedures in the advancement of care for patients with PD, and the importance of neuropsychological and psychological assessment and intervention for patients, families and carers. It also highlighted the skill and innovation with which the surgeons work and the level of care and respect with which the medical and nursing care teams care for the patients. However, above all, the bravery of those patients and their families who live with PD, and those who have undergone DBS surgery and have allowed the advancement of surgical technique and scientific understanding from their treatment has been the most striking.

3.2 Research Approach (Choices made in research)

3.2.1 Inclusion/ exclusion criteria

The original inclusion criteria for patient participation in the study were:

- Participants should be right handed and perform tasks using their right hand.
- Surgical patients to be included will be minimum 6 months post surgery.
- Only surgical patients with a good response to DBS and substantial improvement of clinical symptoms and post-surgery MRI evidence of correct positioning of the electrodes will be included.
- Surgical patients will ideally have little tremor with stimulators off.
- General good health other than PD.

The exclusion criteria for both patients and controls in the study were:

- Current or historical psychiatric illness.
- The presence of any other neurological illness, both current and historical.

These criteria were chosen so as to ensure that the effects that were being studied were the result of STN DBS. These criteria maximised this by ensuring a homogenous patient sample, who gained sufficient post-operative relief from motor symptoms and therefore, in whom STN DBS was clinically successful; who were beyond the period when acute side-effects occur and did not have additional conditions that could influence the results. However, during the course of the research it was necessary to amend these criteria for patient inclusion, as due to the small patient population, the limited numbers of patients who could tolerate completing these tasks “off” stimulation and the time restrictions of the study.

3.3 Methodological / conceptual issues

3.3.1 Patient Handedness

On the basis of the aforementioned limitations, due to patient eligibility to participate in the study and time limitations, left-handed patients were also included in the study. The ratio of right handed to left handed patients was 60:40. The necessity of using both right and left handed patients in the study may have had an impact on the results obtained, as all patients completed tests with their right hand. Differences in dominant handedness may complicate the interpretation of results, as participants who used their non-dominant hands may have had slower reaction times on that basis. However, it was

necessary for patients to only use their right hand as this controlled for any effects of disease laterality (i.e. PD symptoms are generally worse on one side than the other).

3.3.2 Recruitment

As Deep Brain Stimulation (DBS) is still in relative infancy and undergoing further development, the choices made regarding inclusion and exclusion criteria for the patient involved were not only based upon scientific principals but also had to take into consideration the ethical considerations that working with this group brought up. As the numbers of patients who have received this surgery were relatively few, it was important for me to consult with my supervisor and her post-doctoral research fellow to consider who may be appropriate to approach for inclusion in the study. As a result of this surgery being a relatively recent surgical development of which little is known about the long term consequences, the patients who receive it are often asked to participate in research. Therefore during the course of the study it was decided that that my supervisor's research fellow would initially approach the remainder of the identified patients to inform them of the study and enquire as to whether I could contact them to be involved. The research fellow was known to many of the patients, as she had also conducted their pre-operative clinical assessments, so this ensured that someone known to them would approach them in the first instance.

3.3.3 Clinical Measures

During the study it became apparent that the clinical measure questionnaires that were used to obtain demographic and clinical information about patients and controls were unnecessarily extending the length of the assessment. Many of the participants travelled

long distances to be involved in the study and it was necessary, therefore, to use their time most effectively and as the PD patients were undergoing the off stimulation condition, it was important to not tire them out. Therefore during the course of the study it was necessary to begin posting the questionnaires out to patients prior to the study date for them to complete either the night prior to or on the morning of the study.

3.4 How my understanding of the phenomenon has changed

Throughout this research I have continued to develop my understanding of Parkinson's disease, on a psychological and neuroscientific level. I have learnt much about the uses of reaction times in the assessment of brain function and the complex interaction between reward mechanisms and reaction times in this area.

In the context of this research I have had the opportunity to learn about the basal ganglia and neurosurgery in greater detail. Although daunting at first, this has given me a greater understanding of the role of psychology and neuropsychology in this area, both at a neuropsychological level in the assessment of preoperative and postoperative functioning and at the psychological level. This has highlighted to me the importance of ongoing psychological services for PD patients and their families, in relation to contemplating surgery, living with the disease and coping with the psychological symptoms that can often accompany it.

I have also taken much from this study in terms of learning more about the broader context of research and the political and systemic environment in which it takes place. I have developed a better understanding of the limitations but also opportunities of

research, especially within the context of simultaneous clinical work. I have also gained more of an appreciation for the importance and application of psychological research in clinical settings, and specifically within neurological settings, where the patients psychological well being and that of the family is so closely tied to their neurological status.

3.5 Strengths and limitations of the research

In this study I was able to focus on STN DBS both on and off stimulation in a very rare group. Therefore, this study contributes to our understanding of a currently small, yet important field that will no doubt have broader impact in coming years, as surgical techniques are refined and applied to a wider PD population. Twelve patients participated, with ten successfully completing the study. Although this was a smaller number than initially intended, it is still a reasonable sample size relative to the patient population, especially considering the nature of the study, which entailed the patients enduring their worst “off” periods (both off medication and off stimulation), and the limited time available to complete the study.

However, there were limitations in this study also. One such limitation was the switching off of patients stimulators. In order to cause as little discomfort as possible to patients and to comply with the ethical considerations of the study patients were switched off stimulation for an average of approximately 45 minutes. I relied on the patients to determine when they were “off” fully, usually waiting approximately ten minutes until commencing testing. Other studies however, had longer duration “off” periods to ensure patients were off stimulation and that performance was not the result

of any residual effects of stimulation e.g. Ellrichmann et al (2008) turned patients off stimulation one hour prior to the beginning of testing. This was not possible in this study, however the findings obtained here may have been more robust if we had implemented this approach.

3.5.1 Elements of study I would change

On the basis of the aforementioned weaknesses of this research, elements of the study I would change would include increasing the sample size and switching off the patients stimulators for a longer duration prior to testing. Although the patient sample obtained was reasonable I would increase the numbers of patients included in the sample if possible.

Other changes I would make to the study would be to use imaging techniques including functional magnetic resonance imaging (fMRI), or Positron Emission Tomography (PET) in order to determine the specific areas of the basal ganglia and frontal cortex that were responding to reward and if this differed under stimulation conditions. This may enable us to draw more firm conclusions regarding the nature of the influence of stimulation on the frontal-subcortical circuits.

3.6 Clinical and scientific implications

The results found here indicate that STN DBS is a clinically successful technique that can ameliorate the debilitating motor symptoms of PD and adds to the vast literature to this effect. The results also indicate that PD patients can increase their maximal speed of response in the presence of reward, in the absence of dopaminergic medication, which

has both clinical and scientific implications. Therefore, even in the context of dopamine deficiency patients were able to move faster in response to a motivating stimulus. This points to the role of non-dopaminergic networks, for example the cholinergic system, in motivation, reward responsiveness and movement, as suggested by other authors. Further research is required to assess the nature of the reward system in the context of dopamine deficiency, both at a neurotransmitter and neural circuit level. The results of this study also have implications for our understanding of the frontal-subcortical circuits and the influence of STN DBS on the function of these circuits. The implications will be discussed in the next section, with reference to future research

STN DBS is still a developing technique and there are vast clinical and scientific implications of this. The necessity of research into the non-motor side effects of the surgery are highlighted, as although controversial in the scientific literature, many patients and families report cognitive, functional and emotional difficulties arising after surgical intervention. This highlights the need for ongoing reciprocal research and clinical practice, in order to encourage ongoing research and assessment of the psychological effects of surgery which can be fed-back to surgical teams that are developing the techniques. In this manner, psychological research has an important role in the development of these techniques to the advantage of patient care and the advancement of scientific enquiry.

The high incidence of apathy in the patient group may reflect the influence of STN DBS on apathy in PD. However, it may also reflect apathy resulting from the original disease process. Whether the frequency of apathy in this sample were due to DBS or PD, it still

remains that high numbers of patients with PD and STN DBS have clinical levels of apathy. This is an important clinical issue and highlights the need for assessment and intervention with both patients and families, as apathy is frequently reported as negatively effecting on quality of life and activities of daily living (Pluck & Brown, 2002) and having significant negative impact on patients and families (Temel et al, 2006).

3.6.1 Future directions for research

The results indicate that future studies are required to further investigate the influence of reward on motivational processes both in PD and healthy controls. This would allow for further investigation of the neural circuits that underlie motivational processes in health and disease. Further research on the influence of STN DBS on reward processes is also highlighted due to the high levels of apathy in the current patient sample, which may represent a sub-group of patients rather than reflecting the general population of PD who have undergone STN DBS. As well as focussing on reward-related tasks the importance of using both broad and focal neuropsychological tests is highlighted in order to differentiate the influence of reward on the frontal-subcortical circuits that underlie motivation and cognition. Tests of executive function should be included, to detect if cognitive function and the associated frontal-subcortical “executive” circuits may influence reward responsiveness. Future studies would benefit from a longitudinal approach, looking at pre and post-operative reward responsiveness and motivational/apathy profiles, to determine if any differential effects of reward or stimulation exist within the DBS-treated PD population.

References

- Ellrichmann G, Harati A & Müller T. (2008). Deep brain stimulation improves performance of complex instrumental paradigms. *Eur Neurol*, 60(1):32-6.
- Pluck, G. & Brown, P. (2002). Apathy in Parkinson's disease. *J Neurol Neurosurg Psychiatry*, 73: 636 – 642.
- Temel, Y., Blokland, A., Ackermans, L., Boon, P., Kranen-Mastenbroek, V.H.J.M., Beuls, E.A.M., Soincemaille G.H., & Visser-Vanderwalle, V. (2006). Differential effects of subthalamic nucleus stimulation in advanced Parkinson disease on reaction time performance. *Exp Brain Res*, 169: 389 – 399.

Appendix A.

Ethical Approval

Dr M Jahanshahi
Sobell Department of Motor Neuroscience &
Movement Disorders



Our Ref: 06L 239

Tel:
Fax:

Email:

Website: www.uclh.nhs.uk

7 JULY 2006

Dear Dr Jahanshahi

Study title: ~~Effect of reward on performance in dystonia~~
REC reference: 03/N022

Amendment number: 3
Amendment date: 21 June 2006

Thank you for your letter dated 22 June 2006, the documents received were reviewed at the meeting of the Sub-Committee of the REC held on 6 July 2006 and approved.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Research governance approval

All investigators and research collaborators in the NHS should notify the R&D Department for the relevant NHS care organisation of this amendment and check whether it affects research governance approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

01/N074:

Please quote this number on all correspondence

Yours sincerely

Committee Co-ordinator

E-mail:

Copy to: R&D Department for UCLH

*Enclosures List of names and professions of members who were present at the meeting
and those who submitted written comments*

**The National Hospital for Neurology and Neurosurgery & Institute of Neurology Joint
REC**

Attendance at Sub-Committee of the REC meeting on 06 July 2006

Committee Members:

<i>Name</i>	<i>Profession</i>	<i>Present?</i>	<i>Notes</i>
<i>(Chair)</i>	<i>Consultant Nurse</i>	<i>Y</i>	
	<i>Nurse</i>	<i>Y</i>	



Central Office for Research Ethics Committees (COREC)

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at <http://eudract.emea.eu.int/document.html#guidance>.

To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available at <http://www.corec.org.uk/applicants/apply/amendments.htm>.

Details of Chief Investigator:

Name: Professor Marjan Jahanshahi
Address: Sobell Department of Motor Neuroscience & Movement Disorders

Telephone:
E-mail:
Fax:

Full title of study:	Original: Effect of reward on performance in dystonia Amended: Neuropsychological investigation of the effect of reward on motor performance in Movement Disorders
Name of main REC:	
REC reference number:	01/N074
Date study commenced:	2001
Protocol reference (if applicable), current version and date:	NA
Amendment number and date:	No 3, 21 June 2006

Type of amendment (indicate all that apply in bold)

(a) Amendment to information previously given on the REC application form

No

If yes, please refer to relevant sections of the REC application in the "summary of changes" below.

(b) Amendment to the protocol

No

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

Yes

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Is this a modified version of an amendment previously notified to the REC and given an unfavourable opinion?

No

Summary of changes

Briefly summarise the main changes proposed in this amendment using language comprehensible to a lay person. Explain the purpose of the changes and their significance for the study. In the case of a modified amendment, highlight the modifications that have been made.

If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

The aim of the amendment is to complete the tasks on a new group of patients with Parkinson's disease who have had deep brain stimulation of the subthalamic nucleus. The patients will complete the RT tasks twice, with DBS on or off. The design and procedures for the study remain identical to the previously submitted and approved protocol.

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.

NONE

List of enclosed documents

<i>Document</i>	<i>Version</i>	<i>Date</i>
Revised subject information sheet	3	June 2006

Declaration

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.

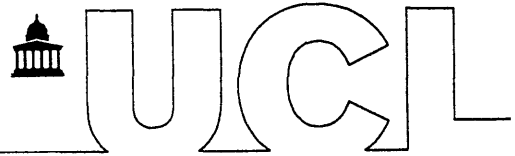
Signature of Chief Investigator:

Print name: Professor Marjan Jahanshahi

Date of submission: 2) 21 June 2006

UCL INSTITUTE OF NEUROLOGY

THE NATIONAL HOSPITAL FOR NEUROLOGY AND
NEUROSURGERY



Sobell Department of Motor Neuroscience and Movement Disorders

Professor Marjan Jahanshahi BSc, MPhil (Clinical Psych), PhD
Head, Cognitive Motor Neuroscience Group

24 November 2005

Dear

Study Ref: 01/N074

Title: Neuropsychological investigation of the effect of reward on motor performance in Movement Disorders

I am writing to obtain approval from the Ethics committee to include assessment of another group of patients as part of this project.

We would like to also assess 16 patients with Parkinson's disease and deep brain stimulation of the subthalamic nucleus as part of this project. Each patient will be assessed twice, with the stimulators on and off. All procedures remain identical to those approved by the Ethics committee. The end date of the project will be extended to June 2006.

I would be grateful if this amendment is considered for approval by Chairman's action.

Yours sincerely,

Professor Marjan Jahanshahi



Institute of Neurology

Sobell Research Department of Motor Neuroscience and Movement Disorders



Professor Marjan Jahanshahi

Institute of Neurology

UCLH Project ID number: 03/N022
Patient Identification Number for this study:
Form version and date: Version 3 June 2006

CONSENT FORM

Title of project: Reaction Time Study in Movement Disorders

Please tick
box

1. I confirm that I have read and understood the information sheet (version 1) for the above study and have had the opportunity to ask questions.
2. I confirm that I have had sufficient time to consider whether or not want to be included in the study
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
4. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Institute of Neurology, where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
5. I agree to take part in the above study.

☐☐☐☐☐

Name of participant

Signature

Date

Name of Parent/Guardian if
participant is under 18 years of age.

Signature

Date

Name of person taking consent

Signature

Date

Professor Jahanshahi (contact details as above)

Name of the researcher to be contacted if there are any problems

Comments or concerns during the study

If you have any comments or concerns you may discuss these with the investigator. If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with the Complaints Manager, Hammersmith hospitals. Please quote the UCLH project number at the top this consent form

1 form for Patient

1 to be kept as part of the study documentation

1 to be kept with hospital notes



Appendix B.

Patient and Control Information sheets and Consent forms



Institute of Neurology

Sobell Research Department of Motor Neuroscience and Movement Disorders



Professor Marjan Jahanshahi

Institute of Neurology

Subject Information Sheet

Reaction Time Study in Movement Disorders

You are invited to participate in a research study conducted at the Institute of Neurology and the National Hospital for Neurology & Neurosurgery.

Aims of the study:

The aim of the study that you are asked to participate in is to find out the effect of Parkinson's disease on different reaction time tasks.

Parkinson's disease is a movement disorder characterised by symptoms such as tremor, rigidity, and postural abnormality. We would like to investigate (i) whether and how the speed of movement initiation and execution is affected in Parkinson's disease and (ii) the similarities and differences between the reaction time performance of three groups of participants (1) patients who have received surgery for treatment of Parkinson's disease, (2) patients who take medication for the treatment of Parkinson's disease and (3) healthy volunteers. Assessing healthy volunteers, like yourself, will help us to assess the nature and degree of slowing of reactions in these patient groups.

What we would like you to do during the study

We would like you to complete the tests described below. The purpose of each test will be explained to you, followed by a demonstration of what you have to do. The important thing is that you try to do your best on all the tests. On some tests such as the questionnaire measures of mood and motivation, there are no right or wrong answers and we are simply interested in your own current experiences. There will be two testing sessions, which will take place on the same day, once in the morning and once in the afternoon. Each session of testing will be about 2 hours with short breaks in between tests.

How will the study be performed?

We would like you to complete a number of relevant tests:

- 1. Measures of mood and motivation:* You will be asked to complete several questionnaires to show us if you are experiencing any disturbance of mood as well as two questionnaires assessing motivation and personality.
- 2. Reaction time tasks:* These tests will measure the speed with which you start and complete simple movements under different conditions that are more or less attention-demanding. For example, in one reaction time task you are asked to press one of the four buttons that is indicated on the screen as quickly as you can.
- 3. Card sorting task:* You are asked to sort a stack of cards as quickly as possible.

Your rights

Your participation in the study is entirely voluntary. You are free to decline to enter or to withdraw from the study at any time without having to give a reason. If you choose not to enter the study, or to withdraw once entered, this will in no way affect your future medical care.

Details about you will be stored on a computer during this research project. All information regarding your medical records will be treated as strictly confidential and will only be used for medical purposes. Your medical records may be inspected by competent authorities and properly authorised persons, but if any information is released this will be done so in coded form so that confidentiality is strictly maintained.

Participation in this study will in no way affect your legal rights.

This research project has been reviewed by the National Hospital for Neurology & Neurosurgery and the Institute of Neurology Ethics Committee.

Contacts:

If you are willing to help with this research study into how Parkinson's disease may affect reaction times or would like to discuss this project further, please contact Andrea Higgins () or Prof Marjan Jahanshahi at the Institute of Neurology on .

Prof M Jahanshahi

Dr S Schneider

Ms Andrea Higgins



Institute of Neurology

Sobell Research Department of Motor Neuroscience and Movement Disorders



Professor Marjan Jahanshahi
Email: m.jahanshahi@ion.ucl.ac.uk
Tel: (44) 020 7837 3611 ext 3055
Fax: (44) 020 7278 9836

Institute of Neurology
Queen Square
London WC1N 3BG
(Box 146)

Subject Information Sheet

Version 3, 21th June 2006

Reaction Time and Deep Brain Stimulation Study

You are invited to participate in a research study conducted at the Institute of Neurology and the National Hospital for Neurology & Neurosurgery.

Aims of the study:

The aim of the study that you are asked to participate in is to compare reaction time in Parkinson's disease when the stimulators are on or temporarily switched off.

In an earlier study we have found that, compared to healthy subjects, reaction times in patients with Parkinson's disease are slow compared to healthy individuals of the same age. In the proposed project, we would like to investigate whether and how the speed of movement initiation and execution in Parkinson's disease is influenced by deep brain stimulation (DBS) of the subthalamic nucleus (STN) by comparing your performance on a series of reaction time tasks that measure of movement initiation and execution when the stimulators are on or temporarily switched off.

What we would like you to do during the study

We would like you to complete the tests described below. The purpose of each test will be explained to you, followed by a demonstration of what you have to do. The important thing is that you try to do your best on all the tests. On some tests such as the questionnaire measures of mood and motivation, there are no right or wrong answers and we are simply interested in your own current experiences. The testing will be about 2 ½-3 hours with short breaks in between tests.

How will the study be performed?

We would like you to complete a number of relevant tests:

1. *Measures of mood and motivation:* You will be asked to complete several questionnaires to show us if you are experiencing any disturbance of mood as well as two questionnaires assessing motivation and personality.
2. *Reaction time tasks:* These tests will measure the speed with which you start and complete simple movements under different conditions that are more or less attention-demanding. For example, in one reaction time task you are asked to press one of the four buttons that is indicated on the screen as quickly as you can.
3. *Card sorting task:* You are asked to sort a stack of cards as quickly as possible.

Why have you been chosen?

You have been invited to participate because you suffer from Parkinson's disease, and you have been implanted with bilateral subthalamic nucleus stimulation. If you agree to participate you will be one of the 12 patients we hope to recruit into the study.

What are the risks and side effects of taking part in the study?

You may encounter some discomfort due to worsening of your parkinsonian symptoms when your stimulators are switched off for a maximum period of 45 to 60 minutes. Your symptoms should be well-controlled again when the stimulators are switched back on.

Your rights

Your participation in the study is entirely voluntary. You are free to decline to enter or to withdraw from the study at any time without having to give a reason. If you choose not to enter the study, or to withdraw once entered, this will in no way affect your future medical care.

Details about you will be stored on a computer during this research project. All information regarding your medical records will be treated as strictly confidential and will only be used for medical purposes. Your medical records may be inspected by competent authorities and properly authorised persons, but if any information is released this will be done so in coded form so that confidentiality is strictly maintained.

Participation in this study will in no way affect your legal rights.

This research project has been reviewed by the National Hospital for Neurology & Neurosurgery and the Institute of Neurology Ethics Committee.

Contacts:

If you are willing to help with this research study into how reaction times in movement disorders are affected or would like to discuss this project further, please contact Andrea Higgins () or Professor Marjan Jahanshahi () at the Institute of Neurology on .

Professor M Jahanshahi

Ms Andrea Higgins